Senate Business, Labor and Economic Affairs

SB 234

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Testimony and Opposition

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My name is Robert Shepard, MD. I am a family practice physician. I practiced in Helena Montana for almost 26 years. I mention this at the outset, to put some context on my comments on this bill to the committee. During that time, I worked with dozens of families with a wide range of problems that had few or no good treatments. I learned and witnessed the struggles that people have with these problems. I always felt it was my duty and job as a physician to guide people through a difficult medical system. Our medical system has great treatments for some diseases and, unfortunately, some bogus and expensive therapies for others. I tried to help patients find the former and avoid the latter. Five years ago, I quit medical practice and began working for New West Heath Services as the medical director. It is in that capacity that I am here today. In this time, I have tried to bring a simple approach to what we do. If it works, we cover it. It is in everyone's interest and less expensive in the long run to use effective therapies. If it doesn't work, we don't cover it. Nothing is more expensive than ineffective therapies.

This bill has a little of both. But before I comment on those parts, I would like to make an observation. What this bill does is specify specific treatments for a specific condition, or group of conditions. This effectively puts the legislature in the position of making a determination of the best and most effective treatments for these conditions. It also means the legislature takes on the responsibility of reviewing treatments that are developed in the future and rewriting the bill to substitute newer and more effective therapies for those in the current bill. This process will be ongoing. This is particularly true for a disease whose primary cause or causes are unknown. And for which there is no comprehensive theory of the neurobiological defects in the brain. While are lots of good ideas and lots of research leads, none of them have been proven, even to the proponents of those theories. In this situation, you can expect ongoing changes in the treatment options, from medications to intensive therapy to computer games. I wish you good luck and enjoyable studies as you go down this path.

Let me agree now, that some intensive therapies, such as Applied Behavior Analysis, and Pivotal Response Training (PRT), which isn't even mentioned in the bill, have been shown to improve the status of some children with Autism, Asperger's disease, and Pervasive Developmental Disorder Not Otherwise specified (PDD NOS). So yes, intensive treatment does help these conditions. This is point number one. This therapy would be covered under the current law

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which mandates parity for some severe mental conditions including autism and because it works. Contrary to some of the comments that allege that insurance companies won't cover this. I really don't see how they could deny it under current Montana law.

However, there are some caveats on the idea that this works. First, it doesn't work for all children. In the best studies, there is improvement in a number of functional areas. But when you look closely at the data, about half (50%) of the children improve substantially and the other half get no benefit or minimal benefit. You can predict, with some certainty, which children will benefit: those with higher IQs, those at a younger age, those with language skills pretreatment, those with higher socialization skills. Those children with rapid acquisition and improvements in IQ after one year were the children that benefited. Not all Children. This bill doesn't allow for stopping therapy in non-responding children.

All of these studies had small numbers of children, usually under 30, with only a couple of studies with 60-70 patients. Most studies were short with durations of a few months. Most studies had only younger children (under 6) in the study.

This bill mandates coverage with no discretion to stop therapy in children for whom it isn't working. It mandates therapy for all age groups when there is not any data suggesting that this approach works in older children or adolescents. There is reason to believe that it would not. And lastly, it mandates maintenance therapy when the benefit for this is also uncertain, or unstudied.

In researching the training required to effectively prescribe and deliver these treatments, primarily Applied Behavioral Analysis, there is another question: Can these therapies be effectively delivered in a community care setting? There are not many studies that address this question. The few studies that do address this question have significant methodological problems. Consequently, it is still uncertain if small communities can reach the same proficiency as the medical centers where most of the testing has been done. Providers need training and certification. That training and certification does exist and there is a website listing certified therapists. According to the website, there are three therapists certified in ABA approaches in Montana: one in Billings, one in Helena and one in Whitefish. I am not certain that there are sufficient qualified resources available to treat all of the children in Montana. In addition, these intensive therapies also require consistent application by all of the people involved in the care of the child. It isn't clear how day care staff and school staff will meet this challenge.

There is at least one treatment suggested in the bill which clearly does not work. This would be dietary therapy. In several reviews I read, every trial of dietary therapy in autism has failed to show that there is a benefit to special diets in autism. Yet this would be covered despite the evidence to the contrary. It isn't clear if other ineffective therapies (such as secretin) would be covered regardless of effectiveness. And what about megavitamins, music therapy, auditory integration therapy, and other discredited therapies. It really isn't clear if these would or would not be mandated by the language in this bill. This is problematic. It is also reflective of the responsibility the legislature has to get the science right with this mandate. If you mandate ineffective therapies, you increase cost and provide no benefit.

One other idea that this bill doesn't address is early screening. It is very important that children with autism are identified early. Most of the studies attest to the importance of early intervention. While there is a state screening program today, it is my understanding that the grant funding that program runs out in a couple of months.

Whatever decision you make, the insurance industry will adapt. In a year or so, we will figure out how much this mandate will cost through direct experience. Remember, Insurance companies don't pay for health care, employers do. Ultimately, the cost will be borne by the businesses in Montana. Be sure to consider them in your decision.

I would like to leave you with one additional thought. There is a bill, Senate Bill 44, which establishes a Health Policy Council. This is just the type of issue that could be discussed in that council. The council could review the established data, discuss this with experts, and take the time to look at the costs and benefits outside of the political process. There is a real need for just such a council and this idea is part of most health care reform plans. We need to carefully review many therapies so that new and proven therapies are not delayed in adoption and that older less effective therapies are dropped. That is the best place for this topic to be considered.

TREATING THE CORE FEATURES OF AUTISM: ARE WE THERE YET?

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A wide variety of nonestablished treatments have been proposed as "cures" for the core features of autism and are used frequently despite having largely escaped scientific scrutiny. In contrast, a growing body of empirical evidence supports the use of a few forms of theory-based and empirically validated treatment for some aspects of the core features of autism. These include behavioral/psychoeducational interventions and specific forms of medication treatment, which can produce significant improvements in communication, social interaction, and problem behaviors that both maintain over time and generalize across settings. While there is no doubt that treatment and educational services for persons with autism have improved over the past 6 decades, it also appears that significant issues remain with respect to (1) the routine application of validated treatments for the majority of cases with autism, (2) the resistance to even validated forms of treatment for a substantial minority of cases with autism, and (3) the extent to which validated treatments effectively treat the specific core features of autism that are most disabling for persons with autism and their families.   © 2004 Wiley-Liss, Inc.
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A s autism is characterized by deficits in language usage, impairments in social reciprocity, and the presence of behavioral rigidity, the primary goal of autism treatment should be the alleviation of these core features. Thus the pressing question when considering the body of treatment research studies in autism is—"*Do available treatments alleviate the core features of autism?*" This has been the central question in systematic reviews of autism and its treatment during the six decades which have now passed since Kanner's [1943] seminal work on the disorder [Eisenberg, 1956; Lockyer and Rutter, 1969; Kanner et al., 1972; Rutter, 1985; Bristol et al., 1996; Howlin et al., 2004]. Review of the large body of published autism treatment studies reveals two general areas with respect to the search for treatments for the core features of autism: (1) a variety of nonestablished treatments that frequently have been proposed as "cures" for the core features of autism but have largely escaped scientific validation and (2) the growing body of empirical evidence on a few forms of theory-based and empirically validated forms of treatment for the core features of autism. In this paper, I will outline the progress that has been made in each of these areas. In addition to reviewing evidence for the efficacy of treatments for autism, I will examine what I term the "depth of intervention effect" question in autism. Specifically, given the range of symptoms that are expressed in autism, how "deeply" do established treatments go in impacting the continuum of impairment within each domain area?

NONESTABLISHED TREATMENTS FOR AUTISM

Parents of children with autism find the disorder to be an unusually mysterious and perplexing condition in which symptoms and behaviors fluctuate with inexplicable rhythms. As such, causes and explanations of autistic behavior are occasionally glimpsed but never fully revealed. Add to this the fact that frequently children with autism demonstrate clear "islands of ability" amidst a sea of disabilities. This can leave parents with a powerful sense that maybe something can be done to "open the door." Parents' hopes for such "cures" are easily amplified by dramatic reporting of anecdotes on television, on the Internet, and in newspapers [Sandler and Bodfish, 2000].

Over the past several decades, many approaches have been serendipitously "discovered," each proposed as a "treatment," and some even boldly hailed as a "cure" for autism via sensational accounts in the media. These include holding therapy, megavitamins, music therapy, auditory integration therapy, facilitated communication, sensory diets, sensorimotor integration therapy, play therapy, Gentle Teaching, experimental brain surgery, immunosuppressant therapy, and secretin to name a few. Few of these were ever promising enough to even progress to rigorous scientific testing in controlled clinical trials despite initial popular media attention [Freeman, 1997]. Some were rigorously tested following parent demands to do so and were found to be ineffective [Sandler et al., 1999; Kern et al., 2004]. Over time these serendipitously discovered approaches to the treatment of autism have failed to achieve the consensus of clinicians or researchers as a legitimate way to alleviate the core features of autism or even to minimize the severity of autistic symptomatology [Campbell et al., 1996; Volkmar et al., 1999]. Although disappointing chapters in the history of autism treatment, the uptake and subsequent release of interest in most of these nonestablished treatment approaches has demonstrated that autism is a disorder that seems to be particularly "at risk" for unfounded claims of treatment [Sandler and Bodfish, 2000].

Because there is no evidence from which individuals who promote treatments for autism can make claims of potential "cures" for autistic children, it is important for clinicians to counsel families to guard against either acting on such claims or increasing their hopes for change to this level.

Despite a lack of empirical evidence or clinical consensus to support their use, there is clear evidence that many parents of children with autism continue to be interested in the use of nonestablished or alternative therapies Aman, Lam, and Collier-Crespin [2003] found that there was considerable use of "alternative medicine" therapies along with standard psychotropic medications in the community treatment of children and adults with autism. In a survey of 121 parents who had enrolled their autistic children in intensive behavior analytic treatment programs ("ABA" treatment), Smith and Antolovich [2000] found that children in ABA treatment programs were also receiving an average of seven supplemental alternative treatment interventions. Interestingly, in the same study these authors reported that parents typically reported that these alternative therapies produced little or no apparent benefit for their autistic child. Although often viewed as benign, alternative therapies can be costly to families in terms of either time or money or both [Sandler and Bodfish, 2000], and those that are more invasive (e.g., alternative medicines, diets, surgeries) have the potential to have adverse effects.

As a part of the overall effort of researching treatments for autism, the examination of these alternative or nonestablished therapies has taken two forms. First, it is clear that research on established treatments now must involve attention to the potential concomitant use of alternative therapies given their popularity among parents [Smith and Antolovich, 2000]. Second, newly proposed alternative treatments are increasingly being subjected to more rigorous scientific evaluations of safety and efficacy. For example, secretin (a peptide hormone that stimulates pancreatic secretion) was proposed as a potential "cure" for autism following a single anecdotal report of its efficacy in 1998. This led to a tremendous amount of media exposure as a potential treatment for autism and considerable parent interest in its use for their children with autism. Within a year of this exposure the first randomized control trial of secretin effects in autism was published [Sandler et al., 1999] show-

ing that secretin had no benefit above placebo on the core symptoms of autism when evaluated under blind conditions. Within the following 3 years, 16 well-controlled studies of secretin treatment in autism have been published, all demonstrating its lack of efficacy. Ironically, secretin is thus the single form of autism treatment that to date has been most rigorously investigated (from the standpoint of randomized clinical trials) and yet there is no rigorous scientific evidence of its efficacy. While it is unfortunate that this research effort did not lead to clues with regard to treatment of the core features of autism, these events demonstrate that the field of autism treatment research has progressed to the point where purported treatments can be rigorously investigated for clinical efficacy in a timely manner.

EMPIRICALLY VALIDATED TREATMENTS FOR AUTISM

In contrast to the disappointments of the various nonestablished treatment approaches, a few forms of treatment have been based in an established theory of autism and have achieved some measure of empirical support and clinical consensus as practical and safe ways to minimize the severity of autistic symptomatology [Bristol et al., 1996; Volkmar et al., 1999]. The two treatment approaches for autism that have amassed the most scientific and clinical support are behavioral/psychoeducational treatment approaches and biomedical treatment approaches. These two approaches evolved from different theoretical orientations to the deficits characteristic of autism. The focus on biomedical causes (i.e., genetic, neurological) lead naturally to a search for medical treatments. In contrast, the focus on abnormalities in behavioral, emotional, and cognitive development lead to an emphasis on psychological or behavioral interventions [Rutter, 1985]. However, although both theoretical approaches make claims with respect to putative etiological and pathophysiologic factors, the pathogenesis of autism has remained largely unknown. For this reason, existing empirically validated treatments for autism are largely symptomatic in nature. Thus, clear empirical validation exists for specific forms of behavioral and medical treatment for particular autistic symptoms within specific core deficit areas rather than as overall forms of treatment for all of the core deficits of autism.

Behavioral/Psychoeducational Treatments for Autism

Conceptual model

The first conceptualization of autism within a behavioral framework was made by Ferster [1961], who hypothesized that some of the acquired behavioral deficits seen in autism might develop due to a deficiency in acquired (i.e., social) reinforcers. Logically, children with social deficits of whatever origin would not naturally acquire adaptive behaviors that other children learn incidentally via natural social consequences. This was followed by empirical demonstrations that behaviors characteristic of each of the core domains of autism could be related in a lawful manner to certain explicit environmental changes [Ferster and DeMyer, 1961], a finding that has now been replicated in hundreds of published studies [Matson et al., 1996; Bregman, 1997]. Of importance in this approach is a clear distinction between the factors responsible for the etiology of autism (presumably genetic and neurobiological) and those factors responsible to for development of the abnormal behaviors associated with autism (presumably environmental and psychological) [Lovaas et al., 1973; Lovaas and Smith, 1989]. This conceptualization, based on the established scientific principles of learning theory, supported the application of learning-based intervention techniques as forms of treatment for both the deficit features of autism (e.g., cognitive, language, social) and the expressed behavioral features of autism (e.g., repetitive behaviors, problem behaviors) (Wolf et al., 1964; Lovaas et al., 1966].

The published behavioral treatment literature that has arisen based on the operant learning model involves the application of the standardized methods of behavioral science to examine and demonstrate treatment effects. Key features of this empirical approach are (1) operational definition of observable target behaviors, (2) definition of behavioral antecedents and consequents that make explicit the functional relationship between the treatment environment and the target behavior, (3) a task analysis that explicitly defines the treatment procedure, and (4) a measurement system for quantifying the acquisition, maintenance, and generalization of the target behavior [Rogers, 2000]. The goal of this methodology is to ensure that effective elements of a treatment procedure can be reliably identified by researchers, tested in replication studies by other researchers, and then reliably and practically ap-

plied by treatment agents (e.g., parents, teachers).

A key feature of the behavioral/ psychoeducational approaches that have been developed to treat autism is an understanding of the unique ways that children with autism tend to interact with their environment and an appreciation of how they benefit from structured, planned, and predictable presentation of stimuli and events [Schopler et al., 1971, 1982]. Accordingly, several models of behavioral/educational treatment for autism have been established (e.g., TE-ACCH, ABA/Discrete Trial Training, Pivotal Response Training, Incidental Teaching) that incorporate elements of this structured learning approach. Other critical programmatic components of effective behavioral/educational models for treating autism that have been identified [Dawson and Osterling, 1991; Howlin, 1998; Wolery, 2000] include the use of a defined curriculum, attention to ensuring predictability and use of routines, the use of generalization strategies, the use of supportive transitions across programs, and high intensity of learning opportunities. Also, family involvement in the treatment planning and implementation process has been incorporated as an essential piece of effective behavioral/educational treatment programs [Schopler and Reicler, 1971].

Communication intervention studies

The treatment of verbal and nonverbal communication deficits has been one of the main areas of research on the behavioral/educational treatment of autism. Under typical conditions, approximately 50% of children diagnosed with autism remain nonverbal [Prizant, 1983]. In contrast to this, studies have indicated that as many as 90% of children with autism can learn to use verbal communication as a primary means of communicating with others when established behavioral/educational interventions designed for teaching language are used before age 5 [McEachin et al., 1993; McGee et al., 1994; Koegel, 1995; Smith et al., 1997; Kern-Koegel, 2000]. Initial behavioral interventions for treating language impairments in autism focused on a structured clinic-based or home-based discrete trial (or "drill") format. While clearly effective in both teaching language and promoting more typical patterns of adaptive behavioral development, the discrete-trial language intervention approach did not promote generalization of language use beyond training settings and it also proved difficult to implement with fidelity in routine

settings [Volkmar et al., 1999; Koegel, 2000; Bibby et al., 2001]. In response to these limitations, approaches have been developed to teach language use more efficiently, more effectively, and more durably in naturally occurring settings (e.g., inclusive preschools and schools, routine home and community settings) [Koegel, 2000]. These natural language teaching approaches involve the inclusion of specific motivational procedures, a focus on following the child's lead, the provision of frequent opportunities for child-initiated expressive language in the natural environment throughout the child's day, and the inclusion of parents, teachers, and peers as therapists [Warren et al., 1984; Charlop et al., 1985; Koegel et al., 1987; Yoder et al., 1993; Koegel, 2000].

Researchers have referred to communication as a "pivotal" behavior that can significantly influence other features of autism. This is based on data that indicates effective language training can lead to generalized (i.e., nontargeted) improvements in social skills [Lovaas et al., 1973; Koegel and Frea, 1993; Dawson and Osterling, 1996; Rogers, 1998], repetitive behaviors [Lovaas et al., 1973], and nonspecific problem behaviors such as noncompliance; self-injury, and aggression [Lovaas et al., 1973; Carr and Durand, 1985; McEachin et al., 1993; Koegel et al., 1999].

A key feature of the language deficits characteristic of autism is that children with autism lack spontaneous verbal and nonverbal initiations even after successful language training has resulted in verbal language as the primary form of the child's communication. While pretreatment intelligence quotient (IQ) and the presence of functional speech before age 5 have long been purported to be the phenotypic characteristics associated with the most favorable outcomes following early intervention in autism [Freeman et al., 1985; Gillberg and Steffenburg, 1987], more recent research suggests that these features are correlates of the level of social-communicative initiations (e.g., initiated joint attention) that may be a more powerful prognostic indicator [Mundy and Crowson, 1997; Koegel et al., 1999; Koegel, 2000]. Accordingly, more recently researchers have developed treatments (1) to increase the generalized use of self-initiated protodeclaratives in prelinguistic children with pervasive developmental disorders [Yoder and Warren; 1999] and (2) to increase the social initiations and spontaneous verbalizations in verbal children with autism [Warren et al., 1984].

Research has also demonstrated that behavioral/educational interventions can be effective in teaching lower-functioning (i.e., IQ < 50) nonverbal children with autism to communicate functionally using augmentative and alternative communication devices (AACs) such as sign language, photographs, communication books, computerized devices, and picture exchange systems [Carr and Kologinsky, 1983; Reichle et al., 1996; Bondy and Frost, 1998]. Although nonverbal children with autism can show substantial gains in prompted use of AACs, there is evidence that such use may not often generalize to untrained settings and that spontaneous communication continues to be a problem for these children [Mirenda and Mathy-Laikko, 1989; Udwin and Yule, 1990].

Social intervention studies

The social deficits of autism have also been the focus of many behavioral/ educational research studies. A wide variety of social interventions for children and adults with autism have been developed and tested in controlled behavioral studies [Rogers, 2000]. Behavioral methods have been shown to be effective in teaching child–parent social interactions [Dawson and Galpert, 1990], child–other adult social interactions [Oke and Schreibman, 1990; Stahmer, 1995], and child–peer social interactions [Strain et al., 1979; Danko et al., 1998]. Social intervention studies have demonstrated that a variety of teaching methods effectively increase social skills (e.g., direct instruction, peer tutoring, video-modeling, social stories/games, scripted self-management) and that such methods are effective in both preschool and school-age children with autism [Rogers, 2000]. Although social intervention studies have included the full range of functioning present within the autism spectrum, relatively few studies have focused on improving social behaviors in lower functioning children or adults with autism [Rogers, 2000].

Paralleling trends in the language interventions studies, early social intervention approaches involved analog discrete-trial adult-directed instruction [Simpson et al., 1997] while more recent studies have focused on incidental teaching approaches that utilize naturally occurring social events with regular interaction partners in routine everyday settings. This shift in focus has brought with it concomitant gains in maintenance and generalization of the social skills that are taught for children and adults with autism [Lord and Hopkins, 1986; Koegel and Frea, 1993; Krantz and McClanna-

han, 1998]. Research has also indicated that social skills appear to be pivotal responses that, when trained, can lead to improvements in other nontargeted symptoms of autism, such as verbal and nonverbal communication [Krantz and McClannahan, 1993; Stahmer, 1995] and problematic behavior [Lee and Odom, 1996; Koegel et al., 1992].

Repetitive behavior intervention studies

Behavioral interventions have also been studied as forms of treatment for the repetitive behavior and associated features of autism [Matson et al., 1996; Horner et al., 2002]. In autism, this core area is characterized by a variety of overt behavioral symptoms, including stereotyped motor behaviors (e.g., hand-flapping, body-rocking, object spinning), rituals and routines (e.g., ordering items or events, insisting on sameness), obsessional restricted interests (e.g., nonfunctional consuming interest in train schedules), and also a more general characteristic of rigidity/inflexibility and poor response to novelty [Rutter, 1985; Lewis and Bodfish 1999; Bodfish et al., 2000]. To date, the treatment of the repetitive behavior core features of autism has received far less study than the treatment of the social and communication deficits of autism. Empirical support does exist for three behavioral approaches for treating repetitive behaviors in children and adults with autism: (1) teaching, occasioning, and reinforcing alternative adaptive behaviors (e.g., language/social interventions, differential reinforcement procedures) [Lee and Odom, 1996; Matson et al., 1996; Horner et al., 2002], (2) environmental arrangement or structuring [Schopler et al., 1971; Clark and Rutter, 1981; Goodall and Corbett, 1982], and (3) shaping or graded change [Rutter, 1985; Howlin, 1998].

In contrast to behavioral/educational intervention studies of the social and communication deficits of autism, studies on the treatment of repetitive behaviors have largely involved lower functioning individuals with autism and consequently little is known about treating this core feature in higher functioning persons with autism. Related to this point, the bulk of the literature on treating repetitive behaviors in autism has focused on treating the simple (and perhaps nonspecific) repetitive behaviors such as stereotyped behavior. Thus, at present, we know little about effective methods for the behavioral/educational treatment of the higher-order ritualistic repetitive behaviors and general rigidity/inflexibility that are most characteristic of autism [Lewis and Bodfish, 1999; Turner; 1999].

BIOMEDICAL TREATMENTS FOR AUTISM

Conceptual Model

Biomedical models of autism move beyond the acquired behavioral aspects of autism to focus more broadly on the potential links between the core features as expressed in manifest behavior and the putative neurobiologic systems involved in the etiology and pathogenisis of these core deficits. Basic behavioral research in autism has made it clear that the phenotype of autism is tremendously heterogeneous both between potential subtypes (e.g., Aspergers, high-functioning autism, low-functioning autism, PDD-NOS) and between individual cases within a subtype. Accordingly, neurobiological models of autism have expanded from models focusing on single brain areas of single neurotransmitter systems (e.g., serotonin, dopamine) to a collection of more modular accounts of putative neural circuits (e.g., fronto-striatal system, medial-temporal lobe), the functional integrity of which is presumed to underlie individual differences in patterns of expression of each of the core deficits.

While autism is undoubtedly a brain disorder, the neurobiological basis of autism remains to be identified. The bulk of available neurochemical evidence supports a role for dopamine (DA) systems in the pathogenesis of the stereotyped, repetitive behavior patterns characteristic of persons with autism [Leckman et al., 1980; Lewis and Baumeister, 1982; Gillberg and Svennerholm, 1987; Launay et al., 1987] and a role for serotonin (5HT) systems in the broader pathogenesis of autism [Schain and Freedman, 1961; Campbell et al., 1974; Hoshino et al., 1984; Anderson et al., 1987; McBride et al., 1989]. In both cases, pharmacological treatment studies have contributed significantly to the evidence suggesting involvement of these neurotransmitter systems in autism.

Medication Intervention Studies

There has been considerable interest in a wide range of medications for the treatment of autism. Of the medications suggested, several have been found to only be effective for nonspecific symptoms such as irritability, overactivity, aggression, and self-injurious behavior [King, 2000]. In contrast, dopaminergic and serotonergic agents have been demonstrated to have clinically significant effects on some aspects of the core features of autism when examined in randomized, controlled trials [Volkmar et al., 1999; Lewis and Bodfish, 1999]. This is consistent with the bulk of the existing neurobiological evidence, which suggests that aberrant behavior in autism is mediated in part by alterations in brain 5HT and DA systems [Lewis et al., 1996b; Racusin et al., 1999; Aman et al., 2000].

There is evidence that the older, "typical" antipsychotics and the nonselective serotonin reuptake medications are poorly tolerated by many individuals with autism [Gordon et al., 1993; Campbell et al., 1997]. For this reason, current psychopharmacology treatment research in autism has focused on the newer dopamine-blocking agents (referred to as "atypical" antipsychotics) and the newer serotonin reuptake inhibitors (referred to as selective serotonin reuptake inhibiting agents or SSRIs).

There is reasonable evidence supporting the use of the atypical antipsychotics risperidone and olanzapine in the treatment of some of the behavioral problems associated with autism. The evidence includes several open trials and two placebo-controlled trials of atypical antipsychotics in autism, all reporting significant improvements in at least half of the patients studied [Findling et al., 1997; Horrigan and Barnhill, 1997; McDougle et al., 1997, 1998b; Potenza et al., 1999; Posey et al., 1999b; Malone et al., 2001; McCracken et al., 2002]. However, in these studies most of the improvements were seen in such nonspecific behavioral problems as aggression, self-injurious behavior, irritability, and anxiety. With respect to the core features of autism, improvements were reported for some of the repetitive behavioral features of autism but not for the social or communication deficits. Further, while clearly significant with respect to improvements in behavioral problems in most cases, the atypical antipsychotics are also clearly associated with weight gain and sedation in at least a significant minority of cases treated and for some of whom such side effects become treatment limiting [Aman and Madrid, 1999]. Although atypical antipsychotics are known to produce fewer extrapyramidal side effects (e.g., dyskinesia, akathisia, parkinsonism) than typical antipsychotics (e.g., haloperidol, thioridazine), the acute nature of the majority of the atypical antipsychotic treatment studies in autism does not provide sufficient time to accurately evaluate potential long-term tardive effects (e.g., tardive dyskinesia).

There is also reasonable evidence supporting the use of serotonin reuptake inhibitors in the treatment of older individuals with autism. This evidence includes numerous positive case series and

open studies reporting improvements in autistic adults [Cook et al., 1992; Bodfish and Madison; 1993; Hellings et al., 1996; Brodkin et al., 1997; McDougle; 1998a; Posey et al., 1999a; Buchsbaum et al., 2001]. There also have been four positive double-blind, placebo-controlled trials with SRIs. The SRI clomipramine was shown to reduce repetitive behavior and abnormal social-communication symptoms to a significantly greater degree than the non-SRI comparator desipramine but clomipramine was also associated with significant side effects in several cases [Gordon et al., 1993]. McDougle et al. [1996] showed that fluvoxamine led to significant improvements in the overall functioning of 53% of the 16 people treated, while none of those in the placebo group responded. Fluvoxamine-related improvements were noted in repetitive thoughts and behaviors and maladaptive behaviors. In two additional placebo, double-blind studies, clomipramine produced clinically significant (>50%) reduction in a variety of repetitive behaviors in adults with PDD and mental retardation. Improvements were noted in repetitive behaviors (e.g., stereotyped motor behaviors, compulsions) as measured by both direct behavioral counts and clinical ratings scales [Lewis et al., 1995, 1996a].

The evidence of the effects of SRIs in children is more equivocal as there have been no randomized controlled trials published to date in children. Published open trial studies with the less selective medication clomipramine have shown inconsistent findings and some have indicated that younger children respond less well [Brasic et al., 1994; McDougle et al., 2000]. Significant improvements have been more consistently observed in open studies of the SSRIs [Steingard et al., 1997; DeLong et al., 1998], including improvements in both repetitive behavior and social-communication symptoms. DeLong and colleagues' study of the effects of fluoxetine in young autistic children is particularly provocative because of the gains in language skills that were reported for children who were receiving concommitant behavioral treatment for language. Improvements in social functioning and increased interest in the environment were reported in an open prospective study of fluoxetine treatment of six children between 4 and 8 years with autism [Peral et al., 1999]. However, these effects have not been replicated to date under blinded, placebo-controlled conditions and concerns have been raised about the tolerability of SSRIs in the pediatric populations [McDougle et al., 2000].

SOCIAL VALIDITY OF TREATMENTS FOR AUTISM

So far, evidence from treatment studies has been considered in support of the empirically validated forms of treatment for autism. Another way to gauge the effectiveness of the existing behavioral and medical interventions is to examine their effects in relation to what is known about the natural course of autism from childhood to adulthood. This provides a necessary degree of social validity to considerations of treatment effectiveness. Existing studies of the natural course of autism have identified the range of possible adult outcomes for persons with autism.

The earliest systematic studies followed adults ($n = 37$) who had been originally diagnosed in the 1950s and 1960s [Rutter and Lockyear, 1967; Lockyear and Rutter, 1969] and found that at follow-up few had acquired speech, almost all had shown declines in IQ, and 75% required institutionalization. In contrast to the early outcome studies, it is now clear that, when specific behavioral/psychoeducational treatments developed for autism are applied with fidelity, most children with autism acquire speech, most exhibit either no change or an improvement in IQ, and few regress to the point of requiring institutionalization [Volkmar et al., 1999]. With respect to medical treatments, as recently as 1985 it was noted that outcomes from medication interventions for autism were "generally disappointing" [Rutter, 1995] but more recently a wider variety of medications have become available and specific medications have been found to be safe and effective for the treatment of some of the behavioral sequelae of autism, including ritualistic repetitive behaviors and also nonspecific problematic behaviors [Aman and Madrid, 1999; Rascusin et al., 1999; King, 2000].

Despite the demonstrated promise of the empirically validated treatments for autism, it is also now clear that there can be a considerable gap between the magnitude of treatment outcomes in well-controlled treatment studies and those obtained as a result of typically available treatment services for persons with autism and their families. For example, in a more recent study of adult outcomes for children with autism ($n = 68$ children who grew up in 1980s and 1990s) Howlin et al. [2004] showed that only 22% achieved a "very good" or "good" outcome while the majority (58%) were rated as having "poor" (46%) or "very poor" (12%) outcomes.

While there is no doubt that treatment and educational services for persons with autism have improved over the past six decades, it also appears that significant issues remain with respect to both the routine application of validated treatments for the majority of cases with autism and the resistance to even validated forms of treatment for a substantial minority of cases with autism. To be sure, to some extent this gap between treatment study and routine service outcomes for persons with autism is related to problems in translating effective treatment procedures from highly controlled experimental settings to routine clinical settings (i.e., problems with treatment fidelity in the real world). However, it is also plausible that these interventions, while effective as treatments at some level, are not typically impacting autism at a deep enough level to produce the kind of socially valid outcomes that are being tracked in these studies of adult outcomes in autism.

DEPTH OF INTERVENTION EFFECTS IN AUTISM

As reviewed above, it is clear that ample experimental evidence exists that persons with autism can learn more appropriate ways of communicating, interacting, and behaving provided that effective behavioral/psychoeducational methods of treatment are used. Importantly, these skills appear to maintain and generalize provided that such behavioral/psychoeducational approaches are adapted to ensure that child-specific motivational procedures are used and learning in natural communication and social interaction settings takes place. Further, it is clear that specific medication treatments can also produce significant improvements in some of the specific behavioral difficulties associated with autism and also can significantly reduce nonspecific behavior and mood problems. However, it is important to consider what can be termed the "depth of intervention effect" question: Do these empirically established forms of behavioral and medication treatment for autism significantly impact those core features that are most characteristic and likewise most disabling for persons with autism?

Answering the "depth of intervention effect" question requires that we can distinguish between symptoms of each core domain that may be present but are not as specific to the autism impairment as other, more specific symptomatic expressions of the core domain. Advances

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in behavioral studies of autism have shed light on the continuum of symptoms that can be impaired within each core area of autism and also which specific symptoms seem to be most characteristic of autistic impairment in general [Rutter, 1985; Tager-Flusberg, 1997; Turner, 1999; Constantino et al., 2000]. In autism, social and communication deficits are joint parts of one of the most characteristic and defining features of autism–social-pragmatics or the social uses of communication [Lord and Hopkins, 1986; Lord and Pickles, 1996; Tager-Flusberg, 1997]. Autistic children often lack empathy and the ability to share other people's feelings and can find it difficult to appreciate social cues and signals [Rutter, 1985; Lord and Magill-Evans, 1995; Bauminger and Kasari, 2000]. As a result of these key social-pragmatic deficits, persons with autism lack social reciprocity and responsiveness to others. In a similar way, features of the repetitive behavior core area of autism can be hierarchically arranged with respect to apparent specificity and resultant functional impact on overall adaptive behavioral development. Lower-order stereotyped behaviors are often present but do not seem to produce the kind of all-encompassing problems that the more general pattern of behavioral rigidity (e.g., inflexibility, resistance to change, need for sameness, restricted interests) seems to produce for persons with autism [Lewis and Bodfish, 1999; Turner, 1999; Bodfish et al., 2000].

Armed with a more complete knowledge of the range of behavioral impairments that exists within the core domains of autism, a more critical appraisal of the effects of empirically validated treatments can be considered. Viewed in this light, key issues in the treatment of the core deficits of autism are whether the effects of existing empirically supported interventions (1) extend beyond discrete aspects of communication behavior (phonological, syntactic, and semantic abilities) to include the functional social use of language, (2) extend beyond simply increasing the frequency of social interactions to affect the more complex social–emotional deficits that are the defining feature of autistic social impairments, and (3) extend beyond simple stereotyped behaviors to include the more complex, higher-order forms of behavioral rigidity that are characteristic of autism. However, as reviewed above, a critical appraisal of findings from both behavioral/educational and medical intervention studies with respect to those core features of autism that seem to be most characteristic of the disorder suggests that these treatments seem to be most effective

in treating relatively simple aspects of the core features of autism (e.g., speech, social interaction, stereotyped behavior) while leaving the more complex phenotypic features untreated in the majority of cases. Consequently, it is not clear whether these aspects of the core features of autism are appreciably improved by the existing empirically validated interventions for autism [Bristol et al., 1996; Koegel, 2000; Rogers, 2000]. Simply put: treatments may bring about less flapping, more words, and more interactions when flexibility, meaning, and friends are what is needed.

Coming full circle to return to the issue of nonestablished "alternative" treatments, one wonders whether to some extent some parents of children with autism sense both the practical limitations of the existing empirically validated interventions and their "shallowness" of effect with respect to the core features of autism. If so, this would at least go partway in helping to explain parents' continued interest in and use of alternative invalidated treatments. To be sure, many parents are satisfied with the effects that the empirically validated behavioral and medication treatments have produced for their children. However, the fact that most parents remain interested in presumably ineffective treatments [Smith and Antolovich, 2000] should humble the research community. It seems reasonable to assume that this reflects several things. First, a deep desire to improve their child's quality of life (and not just to reduce symptom severity). Second, a recognition of the disruptive effects that autism can have on family life in general. And, third, a lack of satisfaction with either the existing treatment options or their availability and typical application in routine practice. To the extent that these reflections are true, it is important to consider these weaknesses of the existing validated forms of treatment as a basis for directing future research designed to discover improved forms of treatment for the core features of autism.

FUTURE DIRECTIONS FOR AUTISM TREATMENT RESEARCH

How can studies of autism treatment move beyond demonstrations of changes in lower-level features of the autistic phenotype to begin addressing mechanisms for producing more meaningful changes in those features of autism that are most disabling? Answers to this question are likely to involve a combination of both continued study of the existing validated forms of autism treatment

and novel lines of treatment research aimed at discovering novel treatment approaches.

Many others have noted the urgent need for more scientifically rigorous studies of the existing forms of autism treatment [Rutter, 1985; Bristol et al., 1996; Lewis and Bodfish, 1999; Lord, 2000]. Most of the research findings in the area of medication interventions are based on open trials with small to modest heterogeneous sample sizes, and most of the research findings in the area of behavioral/educational interventions are based on single-subject designs typically replicated across a small number of poorly characterized cases. To rectify this lack of scientific rigor, methodological improvements that need to be included in future studies are (1) the use of well-chosen and well-specified autism groups based on validated assessment and diagnosis procedures; (2) the inclusion of appropriate control groups and/or control conditions; (3) random assignment to treatment groups/conditions; (4) the use of psychometrically sound standardized outcome measures that have established validity as measures of the core features of autism; (5) the assessment of generality of treatment effects across settings, including those that tend to be problematic for persons with autism; (6) the assessment of the maintenance of treatment effects beyond acute treatment periods; and (7) the use of measures of treatment acceptability (i.e., to families) and cost. In addition, for most of the areas of autism treatment, evidence is lacking on treatments for lower functioning persons. Thus, treatment research focusing on persons with autism and comorbid mental retardation is urgently needed as this subgroup represents up to 70% of the autistic population. The dearth of rigorous treatment studies is beginning to be addressed within the existing network of NIH-funded RUPP (Research Units of Pediatric Psychopharmacology), CPEA (Centers for Programs of Excellence in Autism), and STAART (Studies To Advance Autism Research and Treatment) autism research centers where a variety of well-controlled multicenter behavioral and biomedical intervention studies are currently ongoing.

Along with more rigorous methodologies, there is also a need to address the depth of intervention effect question to begin to determine whether interventions are producing changes in core deficits that are driving symptom expression. This will involve expanding the repertoire of treatment outcome measures from straightforward symptom invento-

ries to more precise measures of core deficits. This could involve using established measures from autism "mechanism" studies (e.g., neurocognitive performance, fMRI, neurochemical markers, behavioral mechanisms) as outcome measures in treatment studies. This would permit within treatment group analyses to determine whether treatment-related symptom changes are associated with changes in outcomes at the level of putative mechanisms. This would provide information on which treatments are simply changing symptom severity and which are more deeply altering core mechanisms.

Novel approaches for treating the core features of autism may lie in efforts to link emerging basic studies of the early development and early identification of autism with existing early intervention approaches. Existing studies of behavioral/educational treatment have shown that early and sustained intervention appears particularly important. Currently, timing of early intervention for autism has been restricted to late infancy/early childhood (e.g., 3–6 years of age) due limitations in clinicians' ability to reliably diagnose autism in early infancy. Work on the accurate early identification of autism is closing this gap between the point in time when the first behavioral and developmental abnormalities are apparent and the clinical diagnosis of autism is made [Stone et al., 1994; Baranek, 1999]. This will permit earlier initiation of the validated forms of autism treatment, with the hope that effective early intervention may impact positively the trajectory of brain and behavioral development during a critical period of development. Also, specific interventions can be designed to directly impact the behavioral features that prove to accurately distinguish infants with autism at an early age (e.g., initiated joint attention). If so, correction of these deficits early on may preclude the development of more abnormal autism-specific patterns of behavior.

Increased integration of behavioral and biological approaches to understanding and treating autism is also likely to yield new insights into autism treatment. One unfortunate side effect of the fact that the two general areas of validated treatments for autism (behavioral, biomedical) emerged from distinct conceptual models and their associated distinct academic disciplines (psychology/education, medicine) is that clinically this conceptual distinction has often lead to a false dichotomy of "pills" versus "skills." It is important that researchers and practitio-

ners alike abandon this false dichotomy of "brain" or "behavior" to develop a more integrated approach to understand autism. Clinical practice suggests that medication treatment rarely works in a vacuum and instead is likely optimized when integrated with behavioral/educational, environmental, and family approaches [Volkmar et al., 1999]. Similarly, those forms of medication treatment that have been shown to be effective in treating some of the features of autism may work synergistically with behavioral/educational interventions to more deeply impact the core features of autism. This could include early intervention efforts as there is preliminary evidence that those medications that are effective in treating older children and adults with autism appear to be safe and effective for the treatment of preschool age children with autism [DeLong et al., 1998; Masi et al., 2003; Namerow et al., 2003]. The interaction between treatment and neurobiology may in fact be bidirectional, with medical treatments potentially impacting behavioral treatments and also behavioral treatments potentially impacting early brain development.

The discovery and development of improved treatments for autism is also more likely to occur by focusing treatment research efforts on specific desirable outcomes for children with autism [Wolery, 2000]. What is desired is children who spontaneously demonstrate more varied, sustained, and generative ways of interacting with their environments and with others. Armed with such experiences such children are more likely to lead more independent and socially integrated lifestyles as adults. Development of interventions that promote characteristics like spontaneity, flexibility, and social understanding is likely to depend on our knowledge of the basic behavioral and neurocognitive processes that give rise to and support such personal characteristics. Thus, basic behavioral studies are needed to identify the patterns of interacting with the social and physical environment that lead autistic children to develop the symptoms we recognize as the phenotype of autism. This will permit a shift from the symptomatic treatment of autism toward a focus on the causal factors that, when untreated, lead to the autistic symptoms.

The science of the treatment of persons with autism has come a long way in the last several decades. It has progressed to the point where much is now known about how to effectively manage many of the devastating symptoms asso-

ciated with the disorder and about how persons with autism can be helped to learn new skills. The hope is that future developments in this area will include not only better studies of existing forms of treatment but also an integration of basic and treatment research studies in an effort to develop novel treatment approaches that more deeply impact the core features of the disorder. ■

REFERENCES

Aman MG, Collier-Crespin A, Lindsay RL. 2000. Pharmacotherapy of disorders in mental retardation [review]. Eur Child Adolesc Psychiatry 9:98–107.

Aman MG, Madrid A. 1999. Atypical antipsychotics in persons with developmental disabilities. Ment Retard Dev Disabil Res Rev 5:253–263.

Aman, MG, Lam KS, Collier-Crespin A. 2003. Prevalence and patterns of use of Psychoactive medicines among individuals with autism in the Autism Society of Ohio. J Austism Dev Disord 33:527–534

Anderson GM, Freedman DX, Cohen DJ, et al. 1987. Whole blood serotonin in autistic and normal subjects. J Child Psychol Psychiatry 28:885–900.

Baranek G. 1999. Autism during infancy: A retrospective video analysis of sensory-motor and social behaviors at 9–12 months of age. J Autism Dev Disord 29:213–224

Bauminger N, Kasari C. 2000. Loneliness and friendship in high functioning children with autism. Child Dev 71:447–456.

Bibby P, Eikeseth S, Martin NT, et al. 2001. Progress and outcomes for children with autism receiving parent-managed intensive interventions. Res Dev Disabil 22:425–447.

Bodfish JW, Madison J. 1993. Diagnosis and fluoxetine treatment of compulsive behavior disorder of adults with mental retardation. Am J Ment Retard 98:360–367.

Bodfish JW, Symons FJ, Parker DE, et al. 2000. Varieties of repetitive behavior in autism: Comparisons to mental retardation. J Autism Dev Disord 30:237–243.

Bondy AS, Frost LA. 1998. The picture exchange communication system. Semin Speech Lang 19:373–390.

Brasic JR, Barnett JY, Kaplan D, et al. 1994. Clomipramine ameliorates adventitious movements and compulsions in prepubertal boys with autistic disorder and severe mental retardation. Neurology 44:1309–1312.

Bregman J. 1997. Behavioral interventions. In: Cohen DJ, Volkmar FR, editors. Handbook of Autism and Pervasive Developmental Disorders, 2nd ed. New York: Wiley. p 606–630.

Bristol MM, et al. 1996. State of the science in autism: Report to the National Institutes of Health. J Autism Dev Disord 26:121–154.

Brodkin ES, McDougle CJ, Naylor ST, et al. 1997. Clomipramine in adults with pervasive developmental disorders: A prospective open-label investigation. J Child Adolesc Psychopharmacol 7:109–121.

Buchsbaum MS, Hollander E, Haznedar MM, et al. 2001. Effect of fluoxetine on regional cerebral metabolism in autistic spectrum disorders: A pilot study. Int J Neuropsychopharmacol 4:119–125.

Campbell M, Armenteros JL, Malone RP, et al. 1997. Neuroleptic-related dyskinesias in autistic children: A prospective, longitudinal

study. J Am Acad Child Adolesc Psychiatry 36:835–843.

Campbell M, Friedman E, DeVito E, et al. 1974. Blood serotonin in psychotic and brain damaged children. J Autism Child Schizophr 4:33–41.

Campbell M, Schopler E, Cueva JE, et al. 1996. Treatment of autistic disorder. J Am Acad Child Adolesc Psychiatry 35:134–143.

Carr EG, Durand VM. 1985. Reducing behavior problems through functional communication training. J Appl Behav Anal 18:111–126.

Carr EG, Kologinsky E. 1983. Acquisition of sign language by autistic children. II. Spontaneity and generalization effects. J Appl Behav Anal 16:297–314.

Charlop MH, Schreibman L, Thibodeau MG. 1985. Increasing spontaneous verbal responding in autistic children using a time delay procedure. J Appl Behav Anal 18:155–166.

Clark P, Rutter M. 1981. Autistic children's responses to structure and interpersonal demands. J Autistic Dev Disord 11:201–217.

Constantino JN, Prezybeck T, Friesen D, et al. 2000. Reciprocal social behavior in children with and without pervasive developmental disorders. J Dev Behav Pedia 21:2–11.

Cook EH, Rowlett R, Jaselskis C, et al. 1992. Fluoxetine treatment of children and adults with autistic disorder and mental retardation. J Amer Acad Child and Adoles Psychiatry 31:739–745.

Danko CD, Lawry J, Strain PS. 1998. Social Skills Intervention Manual packet. Unpublished manuscript.

Dawson G, Galpert L. 1990. Mothers' uses of imitative play for facilitating social responsiveness and toy play in young autistic children. Dev Psychopathol 2:151–162.

Dawson G, Osterling J. 1997. Early intervention in autism. In M. Guralink (Ed.), The effectiveness of early intervention. (pp. 307–326). Baltimore: Paul Brookes.

DeLong GR, Teague LA, McSwain-Kamran M. 1998. Effects of fluoxetine treatment in young children with idiopathic autism. Dev Med Child Neurol 40:551–562.

Eisenberg L. 1956. The autistic child in adolescence. Am J Psychiatry 112:607–612.

Ferster CB. 1961. Positive reinforcement and behavioral deficits of autistic children. Child Dev 32:437–456.

Ferster CB, DeMyer MK. 1961. The development of performances in autistic children in an automatically controlled environment. J Chronic Dis 13:312–345.

Findling RL, Maxwell K, Wiznitzer M. 1997. An open clinical trial of risperidone monotherapy in young children with autistic disorder. Psychopharmacol Bull 33:155–159

Freeman BJ. 1997. Guidelines for evaluating intervention programs for children with autism. J Autism Dev Disord 27 6:641–651.

Gillberg C, Svennerholm L. 1987. CSF monoamines in autistic syndromes and other pervasive developmental disorders of early childhood. Br J Psychiatry 151:89–94.

Goodall E, Corbett JA. 1982. Relationships between sensory simulation and stereotyped behaviour in severely mentally retarded and autistic children. J Mental Defic Res 26:163–175.

Gordon CT, State RC, Nelson JE, et al. 1993. A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder. Arch Gen Psychiatry 50:441–447.

Hellings JA, Kelley LA, Gabrielli WF, et al. 1996. Sertraline response in adults with mental retardation and autistic disorder. J Clin Psychiatry 57:333–336.

Horner RH, Carr EG, Strain PS, et al. 2002. Problem behavior interventions for young children with autism: A research synthesis. J Autism Dev Disord 32 5:423–446.

Horrigan JP, Barnhill LJ. 1997. Risperidone and explosive aggressive autism. J Autism Dev Disord 27:313–323.

Hoshino Y, Yamamoto T, Kaneko M, et al. 1984. Blood serotonin and free tryptophan concentration in autistic children. Neuropsychobiology 11:22–27.

Howlin P. 1998. Practitioner review: Psychological and educational treatments for autism. J Child Psychol Psychiatry 39:307–322.

Howlin P, Goode S, Hutton J, et al. 2004. Adult outcome for children with autism. J Child Psychol Psychiatry 45:212–229.

Kanner L. 1943. Autistic disturbances of affective contact. Nervous Child 2:217–250.

Kanner L, Rodriquez A, Ashenden B. 1972. How far can autistic children go in matters of social adaptation? J Austism Childhood Schizophrenia 2:9–33.

Kern-Koegel L. 2000. Interventions to facilitate communication in autism. J Autism Dev Disord 30:383–391.

Kern JK, Espinoza E, Trivedi MH. 2004. The effectiveness of secretin in the management of autism. Expert Opin Pharmacother 5:379–387.

King BH. 2000. Pharmacological treatment of mood disturbances, aggression and self-injury in persons with pervasive developmental disorders. J Autism Dev Disord 30:439–445.

Koegel LK. 1995. Communication and language intervention. In: Koegel RL, Koegel LK, editors. Teaching Children with Autism: Strategies for Initiating Positive Inteactions and Improving Learning Opportunities. Baltimore: Paul H. Brookes. p 17–32.

Koegel LK. 2000. Interventions to facilitate communication in autism. J Autism Dev Disord 30:383–391.

Koegel LK, Koegel RL, Hurley C, et al. 1992. Improving social skills and disruptive behavior in children with autism through self-management. J Appl Behav Anal 25:341–353.

Koegel LK, Koegel RL, Shoshan Y, et al. 1999. Pivotal response intervention: II. Preliminary long-term outcome data. J Assoc Persons Severe Handicaps 24:186–198.

Koegel LK, Stiebel D, Koegel RL. 1998. Reducing aggression in children with autism toward infant or toddler siblings. J Assoc Persons Severe Handicaps 23:111–118.

Koegel RL, Frea WD. 1993. Treatment of social behavior in autism through the modification of pivotal social skills. J Appl Behav Anal 26:369–377.

Koegel RL, O'Dell MC, Koegel LK. 1987. A natural language paradigm for teaching nonverbal autistic children. J Autism Dev Disabil 17:187–199.

Krantz PJ, McClannahan LE. 1993. Teaching children with autism to initiate to peers: Effects of a script-fading procedure. J Appl Behav Anal 26:121–132.

Krantz PJ, McClannahan LE. 1998. Social interaction skills for children with autism: A script-fading procedure for beginning readers. J Appl Behav Anal 31:191–202.

Launay JM, Bursztejn C, Ferrari P, et al. 1987. Catecholamines metabolism in infantile autism: A controlled study of 22 autistic children. J Autism Dev Disord 17:333–347.

Leckman JF, Cohen DJ, Shaywitz BA, et al. 1980. CSF monoamine metabolites in child and adult psychiatric patients: A developmental perspective. Arch Gen Psychiatry 37:677–681.

Lee S, Odom SL. 1996. The relationship between stereotypic behavior and peer social interactions for children with severe disabilities. J Assoc Severely Handicapped 21:88–95.

Lewis MH, Baumeister AA. 1982. Stereotyped mannerisms in mentally retarded persons: Animal modes and theoretical analyses. In: Ellis NR, editor. International Review of Research in Mental Retardation. New York: Academic Press.

Lewis MH, Bodfish JW. 1999. Repetitive behavior disorders in autism. Ment Retard Dev Disabil Res Rev 4:80–89.

Lewis MH, Bodfish JW, Powell SB, et al. 1995. Clomipramine treatment for stereotypy and related repetitive movement disorders associated with mental retardation. Am J Ment Retard 100:299–312.

Lewis MH, Bodfish JW, Powell SB, et al. 1996a. Clomipramine treatment for self-injurious behavior of individuals with mental retardation: A double-blind comparison with placebo. Am J Ment Retard 100:654–665.

Lewis MH, Bodfish JW, Powell SB, et al. 1996b. Plasma HVA in adults with mental retardation and stereotyped behavior: Biochemical evidence for a dopamine deficiency model. Am J Ment Retard 100:413–418.

Lockyer L, Rutter M. 1969. A five- to-fifteen year follow-up study of infantile psychosis: III. Psychological aspects. Br J Psychiatry 115:865–882.

Lord C. 2000. Achievements and future directions for intervention research in communication and autism spectrum disorders. J Autism and Dev Disord 30:393–398.

Lord C, Hopkins JM. 1986. The social behavior of autistic children with younger and same age nonhandicapped peers. J Autism Dev Disord 16:249–262.

Lord C, Magill-Evans. 1995. Peer interactions of autistic children and adolescents. Dev Psychopathol 7:611–626.

Lovaas OI, Berberich JP, Perloff BF, et al. 1966. Acquisition of imitative speech in schizophrenic children. Science 151:705–707.

Lovaas OI, Koegel R, Simmons JQ, et al. 1973. Some generalization and follow-up measures on autistic children in behavior therapy. J Appl Behav Anal 6:131–166.

Lovaas OI, Smith T. 1989. A comprehensive behavior theory of autistic children: Paradigm for research and treatment. J Behav Ther Exp Psychiatry 20:17–29.

Malone RP, Cater J, Sheikh RM, et al. 2001. Olanzapine versus haloperidol in children with autistic disorder: An open pilot study. J Am Acad Child Adolesc Psychiatry 40:887–894.

Masi G, Cosenza A, Mucci M, et al. 2003. A 3-year naturalistic study of 53 preschool children with pervasive developmental disorders treated with risperidone. J Clinical Psychiatry 65:1039–1046,

Matson JL, Benavidez DA, Compton LS, et al. 1996. Behavioral treatment of autistic persons: A review of research from 1980 to the present. Res Dev Disabil 17:433–465.

McBride PA, Anderson GM, Hertzig ME, et al. 1989. Serotonergic responsivity in male young adults with autistic disorder: Results of a pilot study. Arch Gen Psychiatry 46:213–221.

McCracken JT, McGough J, Shah B, et al. Research Units on Pediatric Psychopharmacology Autism Network. 2002. Risperidone in

children with autism and serious behavioral problems. New Eng J Medicine 347:314–321.

McDougle CJ, Brodkin ES, Naylor ST, et al. 1998a. Sertraline in adults with pervasive developmental disorders: A prospective open-label investigation. J Clin Psychopharmacol 18:62–66.

McDougle CJ, Holmes JP, Bronson MR, et al. 1997. Risperidone treatment of children and adolescents with pervasive developmental disorders: A prospective open-label study. J Am Acad Child Adolesc Psychiatry 36:685–693.

McDougle CJ, Holmes JP, Carlson DC, et al. 1998b. A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. Arch Gen Psychiatry 55:633–641.

McDougle CJ, Naylor ST, Cohen DJ, et al. 1996. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. Arch Gen Psychiatry 53:1001–1008.

McEachin JJ, Smith T, Lovaas OI. 1993. Long-term outcome for children with autism who received early intensive behavioral treatment. Amer J Mental Retard 97:359–372.

Mirenda P, Mathy-Laikko P. 1989. Augmentative and alternative communication applications for persons with severe communication applications for persons with severe congenital communication disorders: An introduction. AAC Augmentative Altern Commun 5:3–13.

Mundy P, Crowson M. 1997. Joint attention and early social communication: Implications for research on intervention with autism. J Autism Dev Disord 27:653–676.

Namerow LB, Thomas P, Bostic JQ, et al. 2003. Use of citalopram in pervasive developmental disorders. J of Dev Behav Pediatrics 24:1–7.

Oke NJ, Schreibman L. 1990. Training social initiations to a high-functioning autistic child: Assessment of a collateral behavior change and generalization in a case study. J Autism Dev Disabil 20:479–497.

Peral M, Alcami M, Gilaberte I. 1999. Fluoxetine in children with autism. J Am Acad Child Adolesc Psychiatry 38:1472–1473.

Prizant BM. 1983. Language acquisition and communicative behavior in autism: Toward an understanding of the "whole" of it. J Speech Hear Disord 48:296–307.

Posey DI, Litwiller M, Koburn A, et al. 1999a. Paroxetine in autism. J Am Acad Child Adolesc Psychiatry 38:111–112.

Posey DJ, Walsh KH, Wilson GA, et al. 1999b. Risperidone in the treatment of two very young children with autism. J Child Adolesc Psychopharmacol 9:273–276.

Potenza MN, Holmes JP, Kanes SJ, et al. 1999. Olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: An open-label pilot study. J Clin Psychopharmacol 19:37–44.

Racusin R, Kovner-Kline K, King BH. 1999. Selective serotonin reuptake inhibitors in intellectual disability. Ment Retard Dev Disabil Res Rev 5:264–269.

Reichle J, McEvoy M, Davis C, et al. 1996. Developing preservice and in-service training of early interventionists to serve preschoolers who engage in challenging behavior. In: Koegel LK, Koegel RL, Dunlap G, editors. Positive Behavioral Support. Baltimore: Paul H. Brookes. p 227–2164.

Rodriquez A, Ashenden B. 1972. How far can autistic children go in matters of social adaption? J Autism Child Schizophr 2:9–33.

Rogers S. 1998. Empirically-supported comprehensive treatments for young children with autism. J Clin Child Psych 27:168–179

Rogers SJ. 2000. Inteventions that facilitate socialization in children with autism. J Autism Dev Disord 30 5:399–409.

Rumsey JM, Rapoport JL, Sceery WR. 1985. Autistic children as adults: Psychiatric, social, and behavioral outcomes. J Am Acad Child Psychiatry 24:465–473.

Rutter, M. 1985. The treatment of autistic children. J Child Psychol Psych 26:193–214.

Rutter M, Lockyer L. 1967. A five to fifteen year follow-up study of infantile psychosis: I. Description of the sample. Br J Psyhiatry 113:1169–1182.

Sandler AD, Bodfish JW. 2000. Placebo effects in autism: Lessons from secretin. J Dev Behav Pediatrics 21:347–350.

Sandler AD, Sutton KA, DeWeese J, 1999. Lack of benefit of a single dose of synthetic human secretin in the treatment of autism and pervasive developmental disorder. N Engl J Med 341:1801–1806.

Schain RJ, Freedman DX. 1961. Studies on 5-hydroxindole metabolism in autistic and other mentally retarded children. Disabil Rehabil 58:315–320.

Schopler E, Brehm S, Kinsbourne M, et al. 1971. Effect of treatment structure on development in autistic children. Arch Gen Psychiatry 24:415–421.

Schopler E, Mesibov G, Baker A. 1982. Evaluation of treatment for autistic children and their parents. J Amer Acad Chld Adoles Psychiatry 21:262–267.

Schopler E, Reichler RJ. 1971. Parents as cotherapists in the treatment of psychotic children. J Autism Childhood Schizophrenia 1:87–102.

Simpson RL, Myles BS, Sasso GM, et al. 1997. Social Skills for Students with Autism, 2nd ed. Reston, VA: Council for Exceptional Children.

Smith T, Antolovich M. 2000. Parental perceptions of supplemental interventions received by yound children with autism in intensive behavior analytic treatment. Behavioral Interventions 15:83–97.

Smith T, Eikeseth S, Klevstrand M, et al. 1997. Intensive behavioral treatment for preschool-

ers with severe mental retardation and pervasive developmental disorder. Am J Ment Retard 102:238–249.

Stahmer AC. 1995. Teaching symbolic play skills to children with autism using pivotal response training. J Autism Dev Disord 25:123–142.

Steingard RJ, Zimnitzky B, DeMaso DR, et al. 1997. Sertraline treatment of transition-associated anxiety and agitation in children with autistic disorder. J Child Adolesc Psychopharmacol 7:9–15.

Stone WL, Hoffman EL, Lewis SE, et al. 1994. Early recognition of autism: Parental reports vs clinical observation. Archives of General Psychiatry 148:174–179.

Strain PS, Kerr MM, Ragland EU. 1979. Effects of peer-mediated social initiations and prompting/reinforcement procedures on the social behavior of autistic children. J Autism Dev Disord 9:41–54.

Tager-Flusberg H. 1997. Perspectives on language and communication. In D. Cohen & F. Volkmar (Eds.), Handbook of autism and pervasive developmental disorders (2nd ed., pp. 572–605). New York: Wiley.

Turner M. 1999. Annotation: Repetitive behavior in autism: A review of psychological research. J Child Psychol Psych 40:839–849.

Udwin O, Yule W. 1990. Augmentative communication systems taught to cerebral palsied children: A longitudinal study: I. The acquisition of signs and symbols, and syntactic aspects of their use over time. Br J Disord Commun 25:295–309.

Volkmar F, Cook EH Jr, Pomeroy J, et al. 1999. Practice parameters for the assessment and treatment of children, adolescents, and adults with autism and other pervasive developmental disorders. American Academy of Child and Adolescent Psychiatry Working Group on Quality Issues. J Am Acad Child Adolesc Psychiatry 38:32S–54S.

Warren SF, McQuarter RJ, Rogers-Warren AK. 1984. The effects of teachers mands and models on the speech of unresponsive language-delayed children. J Speech Hear Disord 49:43–52.

Wolery M. 2000. The environment as a source of variability: Implications for research with individuals who have autism. J Autism Dev Disord 30:379–381.

Wolf M, Risley T, Mees H. 1964. Application of operant conditioning procedures to the behavior problems of an autistic child. Behav Res Ther 1:305–312.

Yoder PJ, Kaiser AP, Alpert C, et al. 1993. Following the child's lead when teaching nouns to preschoolers with mental retardation. J Speech Hear Res 36:158–167.

Yoder PJ, Warren SF. 1999. Facilitating self-initiated proto-declaratives and proto-imperatives in prelinguistic children with developmental disabilities. J Early Intervent 22:79–76.

Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder

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Autism Speaks

Abstract

Advances in the fields of cognitive and affective developmental neuroscience, developmental psychopathology, neurobiology, genetics, and applied behavior analysis have contributed to a more optimistic outcome for individuals with autism spectrum disorder (ASD). These advances have led to new methods for early detection and more effective treatments. For the first time, prevention of ASD is plausible. Prevention will entail detecting infants at risk before the full syndrome is present and implementing treatments designed to alter the course of early behavioral and brain development. This article describes a developmental model of risk, risk processes, symptom emergence, and adaptation in ASD that offers a framework for understanding early brain plasticity in ASD and its role in prevention of the disorder.

Autism spectrum disorder (ASD) is a life-long developmental disorder characterized by qualitative impairments in social and communication behavior and a restricted range of activities and interests. ASD is estimated to affect 1 in 150 persons; thus, it is no longer considered a rare disorder (Kuehn, 2007).

During the past three decades, conceptualizations of ASD have changed dramatically. Whereas autism previously was considered a disorder with an extremely poor prognosis with only 50% of individuals developing spoken language (see Dawson, 1989), it has now been demonstrated that 75–95% of children who receive early intensive behavioral intervention develop useful speech by age 5 (Lovaas, 1987; McGee, Morrier, & Daly, 1999; for a review, see Rogers, 1998). Three separate groups have now reported that a significant proportion of children receiving intensive intervention early in life make outstanding progress, with autism symptoms diminishing and developmental outcomes improving such that these children no longer have evidence of disability (Howard, Sparkman, Cohen, Green, & Stanislaw, 2005; McEachin, Smith, & Lovaas, 1993; Sallows & Graupner, 2005).

Rapid advances in the fields of cognitive and affective developmental neuroscience, developmental psychopathology, neurobiology, genetics, and applied behavior analysis have contributed to a more optimistic outcome for individuals with ASD. These advances have led to new methods for early detection and more effective treatments. For the first time, prevention of ASD is plausible. Prevention will entail detecting infants at risk before the full syndrome is present and implementing treatments designed to alter the course of early behavioral and brain development. To provide a framework for understanding early brain plasticity in ASD and its role in prevention of

the disorder, Dawson (Dawson & Faja, in press; Dawson, Sterling, & Faja, in press) has proposed a developmental model of risk, risk processes, symptom emergence, and adaptation in ASD. This model posits that there are genetic, environmental, and phenotypic risk indices that ultimately will allow very early identification of infants who are vulnerable to developing ASD. Identification of such risk indices is a focus of current research in the field. Early genetic and environmental *risk factors* contribute to an atypical trajectory of brain and behavioral development that is manifest in altered patterns of interaction between the child and his/her environment. An important aspect of this altered interaction is a failure on the part of the child to actively engage in early social interaction. Such altered interactions, referred to as *risk processes,* are hypothesized to preclude normal social and prelinguistic input that normally promotes the development of social and linguistic brain circuitry during early sensitive periods, thus serving as mediators of the effects of early susceptibilities on later outcome. Through this mediational process, early susceptibilities contribute to *outcome,* the full autism syndrome, as illustrated in Figure 1a. Risk processes thus amplify the effects of early susceptibilities. Effective interventions target these risk processes.

Numerous authors (e.g., Dawson, Carver, et al., 2002; Dawson, Webb, Wijsman, et al., 2005; Grelotti, Gauthier, & Schultz, 2002; Johnson et al., 2005; Kuhl, 2007; Kuhl et al., 2005; Mundy & Neal, 2001) have described how the development of social and language brain circuitry, its acquisition, organization, and function, results from the interaction between the infant's brain and his or her social environment. Dawson described a developmental model for the normal emergence of social brain circuitry during infancy, stressing the key role of early parent–child interaction in the development of the social brain (Dawson, Webb, & McPartland, 2005; Dawson, Webb, Wijsman, et al., 2005; see Figure 2). In the context of reciprocal social interactions, engagement with a social partner facilitates cortical specialization and perceptual and representational systems for social and linguistic information. Social engagement is required for the well-documented fine-tuning of perceptual systems (Kuhl, 2007). Brain regions specialized for the

perceptual processing of social stimuli, such as the fusiform gyrus and superior temporal sulcus, become integrated with regions involved in reward (e.g., amygdala, ventromedial prefrontal cortex), as well as regions involved in motor actions and attention (cerebellum, prefrontal/cingulate cortex). Reward mechanisms mediated by the amygdala serve to encode and consolidate memories of social–emotional experiences (LaBar, 2007). Through this integrative process, an increasingly complex social brain circuitry emerges. This supports more complex behaviors, such as disengagement of attention, joint attention, intentional communication, and social imitation, behaviors that are typically impaired in ASD.

Altered interactions between the infant and his/her social environment resulting from genetic risk factors might further influence gene expression. Such gene–environment interactions have been demonstrated in animal studies. For example, maternal nursing and grooming behavior by rats early in development produces changes in behavioral and hypothalamic–pituitary–adrenal stress responses that last into adulthood (Caldji et al., 1998; Liu et al., 1997). The mechanism for this change is epigenetic, with maternal behavior directly influencing DNA methylation and chromatin structure (Weaver et al., 2004). Such gene–environment interactions may play a role in ASD as well. Whether and how alterations in early parent–child interaction in ASD influence gene expression is unknown; it is plausible, however, that gene–environment interactions occurring during postnatal life amplify the effects of initial autism susceptibility genes (see Figure 1b).

The model of risk and prevention illustrated in Figure 1 further posits that early intervention can alter the abnormal developmental trajectory of young children with ASD and help guide brain and behavioral development back toward a normal pathway; early intervention targets risk processes involving interaction between the child and his/her social partner (Figure 1c). Brain-based outcome measures will allow us to assess whether such interventions actually result in more normal patterns of brain function and organization.

This article begins by describing the progress that has been made in identifying risk
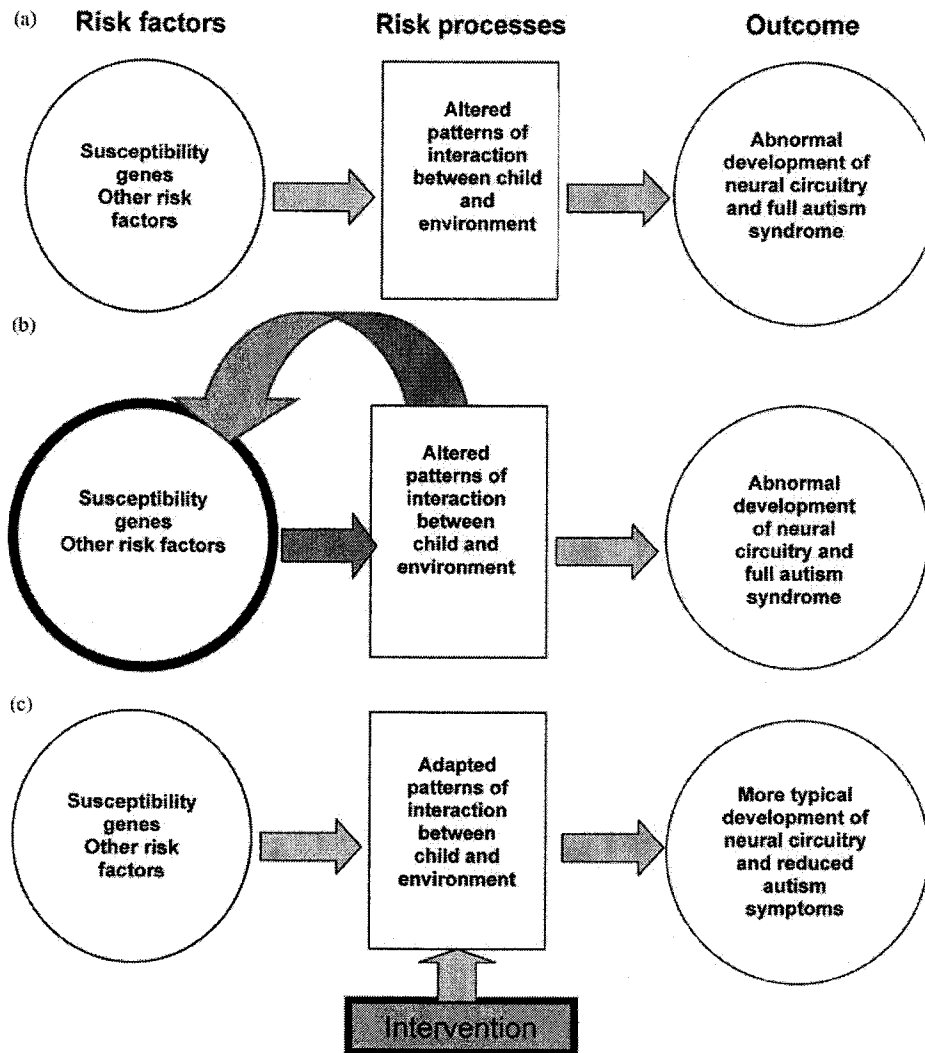
Figure 1. A developmental model of risk factors, risk processes, and outcome in autism.

indices for ASD. Studies aimed at discovering genetic and environmental risk factors will be described first; a brief review of studies describing the behavioral, neurophysiological, and other brain-based risk indices will follow. The role of altered social interactions as a risk process affecting the development of the social brain next will be discussed. Next, infant–toddler interventions aimed at reducing and preventing ASD symptoms will be described. Suggestions will be offered for how brain-based measures of outcome can be incorporated into intervention and prevention studies to allow assessment of the

impact of early intervention on brain function and organization. Finally, factors hypothesized to account for the tremendous variability in response to early intervention will be discussed.

Risk Indices in ASD

Genetic risk factors

One goal of genetic research is to identify infants at increased risk for ASD at birth so that intervention can begin as soon as possible. Although progress in autism genetics is being

Neuropeptides (Oxytocin, Vasopressin)

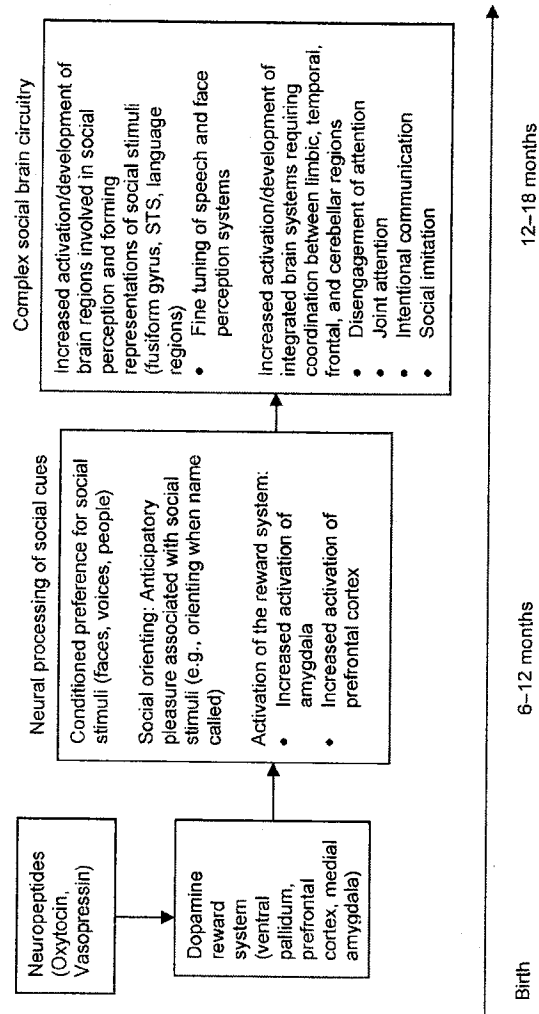**Dopamine reward system (ventral pallidum, prefrontal cortex, medial amygdala)**

Neural processing of social cues

Conditioned preference for social stimuli (faces, voices, people)

Social orienting: Anticipatory pleasure associated with social stimuli (e.g., orienting when name called)

Activation of the reward system:
- Increased activation of amygdala
- Increased activation of prefrontal cortex

Complex social brain circuitry

Increased activation/development of brain regions involved in social perception and forming representations of social stimuli (fusiform gyrus, STS, language regions)
- Fine tuning of speech and face perception systems

Increased activation/development of integrated brain systems requiring coordination between limbic, temporal, frontal, and cerebellar regions
- Disengagement of attention
- Joint attention
- Intentional communication
- Social imitation

Birth

6–12 months

12–18 months

Figure 2. The emergence of social brain circuitry in the first years of life: role of social reward. From "Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: Implications for a model of abnormal development of social brain circuitry in autism," by G. Dawson S. J. Webb, E. Wijsman, G. Schellenberg. A. Estes, J. Munson, and S. Faja. 2005. *Development and Psychopathology, 17,* p. 691. Copyright 2005 Cambridge University Press.

made, the heterogeneity and complexity of the ASD phenotype pose considerable challenges. There is strong evidence for the role of genetics in autism. A substantial number of cases of autism have co-occurring medical conditions, some of which can be linked to identifiable genetic disorders, such as fragile X (Rutter, Bailey, Bolton, & LeCouteur, 1994). The remaining cases are considered idiopathic and likely involve multiple autism susceptibility genes. A multifactor epistatic model with 2–10 contributing loci (Pickles et al., 1995) has been proposed. Concordance rates for monozygotic (MZ) twins are estimated to be 69–95% (Bailey et al., 1995; Folstein & Rutter, 1977a, 1977b; Ritvo et al., 1989; Ritvo, Freeman, Mason-Brothers, Mo, & Ritvo, 1985; Steffenburg et al., 1989), whereas concordance rates for dizygotic (DZ) twins are much lower (approximately 3–8%). Genetic liability extends to a lesser variant, referred to as the "broader autism phenotype." When a broader ASD phenotype (e.g., language and/or social impairment) is considered, concordance rates for twins increase (88–91% for MZ, 9–30% for DZ; Bailey et al., 1995; Folstein & Rutter, 1977b; Steffenburg et al., 1989). Initial estimates of sibling recurrence rates for ASD ranged from 2.8 to 7.0%, significantly higher than the general population (August, Stewart, & Tsai, 1981; Bailey, Phillips, & Rutter, 1996; Smalley, Asarnow, & Spence, 1988). More recent studies of infant siblings, however, have reported much higher recurrence rates (e.g., Landa & Garrett-Mayer, 2006). Bolton et al. (1994) estimated that 12–20% of siblings exhibit a lesser variant of autism. This study was based on a family history method that likely would yield lower rates than the true rate based on direct assessment. Several studies have documented elevated rates of autism related symptoms in immediate family members (Bailey et al., 1995, 1996; Folstein & Rutter, 1977b; Landa, Folstein, & Isaacs, 1991; Landa et al., 1992; Narayan, Moyes, & Wolff, 1990; Toth, Dawson, Meltzoff, Greenson, & Fein, 2007; Wolff, Naravan, & Moyes, 1988). In a large sample of parents of children with autism, Dawson et al. (2005) reported that parents showed a decrement in face recognition ability (performance at an average level) relative to their verbal and visual spatial skills (significantly higher than the

norm in both domains). Current autism genetic linkage studies are using quantitative measures of autistic traits (e.g., quantitative trait locus analyses) to better capture the variation in autism broader phenotype (e.g., Sung et al., 2005).

Several genome-wide linkage studies of autism have been conducted (Auranen et al., 2002; Barrett et al., 1999; Buxbaum et al., 2001; Cantor et al., 2005; International Molecular Genetic Study of Autism Consortium [IMGSAC], 1998, 2001a, 2001b; Lamb et al., 2005; Liu et al., 2001; McCauley et al., 2005; Philippe et al., 1999; Risch et al., 1999; Schellenberg et al., 2006; Shao et al., 2002; Stone et al., 2004; Yonan et al., 2003). Although replicability of signals across studies has generally been weak and promising, if not entirely consistent, evidence of linkage has been found at some chromosome sites, including 1p (Auranen et al., 2002; Risch et al., 1999), 2q (Buxbaum, 2001; Lamb et al., 2005; Liu et al., 2001; Shao et al., 2002), 7q (Barrett et al., 1999; IMGSAC, 1998, 2001a, 2001b; Lamb et al., 2005; Schellenberg et al., 2006), 17q (Cantor et al., 2005; Lamb et al., 2005; Liu et al., 2001; McCauley et al., 2005), and 19q (Philippe et al., 1999; Shao et al., 2002), with the 2q, 7q, and 17q regions giving the strongest signals.

Well over 100 candidate genes have been studied. One promising lead is Engrailed 2 (*En-2*) located on chromosome 7. Animal studies have shown that *EN-2* is expressed in the cerebellum and plays a role in cerebellar development (Cheh et al., 2006; Millen, Wurst, Herrup, & Joyner, 1994). Abnormalities in cerebellar development have been consistently demonstrated in individuals with autism, including reduced Purkinje cells in the cerebellar cortex (Bailey et al., 1998; Courchesne, 1997; 2004; Kemper & Bauman, 1998; Ritvo et al., 1986). En-2 knockout mice have a reduction in Purkinje cells and a decreased size of the cerebellar lobes (Kuemerle, Zanjani, Joyner, & Herrup, 1997; Millen et al., 1994) and display a number of autistic-like behaviors including reduced social play and increased repetitive behavior (Cheh et al., 2006).

The serotonin transporter gene *SLC6A4* also likely has a role in autism genetic susceptibility (reviewed in Devlin et al., 2005). Elevated levels of platelet serotonin (5-HT) have been found in individuals with autism (Rolf, Haarmann,

Grotemeyer, & Kehrer, 1993). Pharmacological treatment in ASD often involves selective 5-HT reuptake inhibitors. 5-HT is involved in guiding neuronal development, modulating sensory input and arousal, sleep, mood, aggression, impulsivity, and affiliation (Lucki, 1998). 5-HT innervates the limbic regions involved in social and emotional behavior. Devlin et al. (2005) reported an excess transmission of the short allele of *5HTTLPR* in individuals with autism. Wassink and colleagues (Wassink et al., 2007) examined the relationship between variability in *5HTTLPR* and early abnormalities in brain growth in autism. Autism has been associated with early enlargement of the brain. In a combined sample from University of Washington and University of North Carolina, Wassink et al. (2007) found that the short (S) allele was strongly associated with increased cerebral cortical gray matter. These findings are the first to establish a direct association between a genetic variation and atypical brain development in autism.

Levitt and colleagues (Campbell et al., 2006) analyzed the gene encoding the MET receptor tyrosine kinase and showed a genetic association between the C allele in the promoter region of the *MET* gene. MET signaling is involved in neocortical and cerebellar development, immune function, and gastrointestinal repair.

Several genetic disorders have been associated with increased risk for ASD or expression of an autistic-like phenotype. These include fragile X syndrome, Rett syndrome, Angelman syndrome, tuberous sclerosis, and neurofibromatosis (see Veenstra-VanderWeele & Cook, 2004, for review). The 15q11–q13 region associated with Angelman syndrome codes for subunits of the gamma-aminobutyric acid A (GABA$_A$) receptor. GABAergic interneurons have a role in establishing the architecture of cortical columns (DeFelipe, Hendry, Hashikawa, Molinari, & Jones, 1990; Peters & Sethares, 1997). The increased prevalence of epilepsy in individuals with autism and 15q11–q13 duplications is consistent with the involvement of GABA. Hippocampal GABA receptor binding in autism is abnormally low (Blatt et al., 2001) as are platelet GABA levels (Rolf et al., 1993).

A combined set of results suggests that autism is a disorder of the synapse (Garber, 2007; Zoghbi, 2003). Zoghbi proposed that autism

results from disruption of postnatal or experience-dependent synaptic plasticity. Rare mutations in the neuroligin 3 and neuroligin 4 genes have been found individuals with autism (Jamain et al., 2003). Neuroligins are proteins expressed on the surface of the postsynaptic neuron that bind to proteins on the presynaptic neuron, neurexin, thus forming the synapse. SHANK3 is another protein that is involved in the neuroligin pathway; SHANK3 mutations have also been found in individuals with autism, accounting for about 1% of cases (Durand et al., 2007). More evidence for involvement of this pathway comes from the findings of the Autism Genome Project (Szatmari et al., 2007) involving collaboration among 50 institutions that pooled genetic data from 1,200 multiplex families. This group found evidence that autism was associated with neurexin 1, which binds to neuroligin at the synapse, and is part of a family of genes that plays a role in the neurotransmitter, glutamate. Glutamate is involved in both synaptogenesis and learning.

New evidence suggests that many individuals with autism have novel deletions and duplications in their genome, most likely arising during meiosis. Sebat et al. (2007) use comparative genomic hybridization on DNA collected from individuals with autism and a control sample, and found that autism was associated with de novo copy number variants (CNVs). CNVs were found in about 10% of the individuals with autism who were from families in which only one person had autism. Zhao and colleagues (2007) have proposed a genetic model of autism in which two genetic types exist: a small minority of cases for whom the risk of autism in males is nearly 50%, and the larger majority of cases for whom male offspring have low risk. In the latter case, sporadic autism is possibly caused by a spontaneous mutation with high penetrance in males and poor penetrance in females. High-risk families, in contrast, are from those offspring (most typically female) who carry a mutation but are unaffected. They are hypothesized to transmit the mutation in dominant fashion to their offspring.

Environmental risk factors

Although it is clear that genetic factors contribute to risk for developing ASD, it is likely that

such genetic factors interact with environmental factors to confer risk (Newschaffer et al., 2007). Among the environmental factors that been proposed are toxins (e.g., environmental pollutants, pesticides, thimerosal in vaccinations) and viruses (e.g., measles in the measles, mumphs, rebulla vaccine, prenatal exposure to influenza infection, rubella, and cytomegalovirus), among others (e.g., Miles & Takahashi, 2007; Tsuchiya et al., 2007). As well, other factors related to the intrauterine environment, including maternal hypothyroxinemia (Roman, in press), maternal influenza (Fatemi et al., 2002; Patterson, 2002; Smith, Garbett, Mirnics, & Patterson, 2007), and exposure to increased levels of sex hormones related to infertility treatment (Croughan et al., 2006) have also been implicated. Investigators have also reported a statistically significant link between a positive family history for allergic/autoimmune disorders and clinical features of ASD, including regression and larger head sizes, as well as atypical prenatal maternal immune responses, suggesting significant genetic and perhaps prenatal contributions autism related to immune function (Croen, Grether, Yoshido, Odouli, & van de Water, 2005; Molloy et al., 2006; Sacco et al., 2007; Zimmerman et al., 2007). Evidence of a worsening developmental trajectory, most dramatically seen in cases of autistic regression (Dawson & Werner, 2005; Dawson et al., 2007), also raises the possibility that postnatal environmental exposures may be of etiologic significance in genetically susceptible children, implicating gene–environmental interactions.

Several studies have revealed evidence of abnormal immune function in autism. Indicators of chronic neuroinflammation have been identified in brains of individuals with autism (Vargas, Nascimbene, Krishman, Zimmerman, & Pardo, 2005) and markers of inflammation and oxidative stress have also been identified in blood and urine of individuals with autism (e.g., Ashwood & Van de Water, 2004; James et al., 2004). Thus, a potentially useful direction in future candidate gene research is to examine genes related to environmental responsiveness, such as those related to cell cycle, DNA repair, and immune and inflammatory response (Herbert et al., 2006).

Summary

In summary, although there is strong evidence for genetic influences in autism, the role of susceptibility genes in autism and the manner in which such genes interact with environmental factors remain an active area of investigation. It has been theorized that, in many instances of ASD, it is likely that multiple genes interact with each other and environmental factors to increase susceptibility to ASD (although see Zhao et al., 2007, for a different view). As Belmonte et al. (2004) point out, although the small effect of each gene by itself makes it difficult to identify specific genes, "the advantage in terms of treatment is that intervening to restore regulation to a single gene or to a small set of genes may diminish the multiplicative effect enough to yield large preventative or therapeutic effects" (p. 650). Because the expression and effects of many genes are influenced by environmental factors, it is possible that early treatment can alter genetic expression, brain development, and behavioral outcome in ASD, especially if intervention can begin early during the infant period before the symptoms of autism are fully manifest. The identification of autism susceptibility genes and other biomarkers will allow detection of infants at increased risk for ASD at birth. It is likely that early detection will eventually involve a combination of biomarkers and phenotypic risk indices. Fortunately, detection using early phenotypic risk indices is rapidly improving as will be discussed next.

Behavioral risk indices

The first studies describing how autism emerges during infancy were based on home videotapes recorded before a diagnosis of autism was made (see Palomo, Belinchón, & Ozonoff, 2006, for review). It was discovered that infants at risk for autism show very few, if any, behavioral symptoms at 6 months; by 12 months, however, core autism symptoms are apparent for many infants (Dawson, Osterling, Meltzoff, & Kuhl, 2000; Osterling & Dawson, 1994; Osterling, Dawson, & Munson, 2002). Failure to respond to name is evident by 8 to 10 months (Werner, Dawson, Osterling, & Dinno, 2000). By 12 months, infants later diagnosed with

autism can be distinguished from typical infants by a failure to respond to name (Baranek, 1999; Osterling & Dawson, 1994; Osterling et al., 2002), decreased looking at the faces of others (Osterling & Dawson, 1994), and low rates of showing things to others and pointing to request and share interest (Adrien et al., 1993; Maestro et al., 2002; Osterling & Dawson, 1994; Osterling et al., 2002; Werner & Dawson, 2005). Poor eye contact and a failure to respond to name also best distinguishes them from infants with developmental delay but without autism (Baranek, 1999; Osterling et al., 2002).

Prospective studies of infant siblings of children with autism have provided new insights into the early development of ASD (e.g., Zwaigenbaum et al., 2005). Estimates of risk rates for autism in siblings range from 3 to 7%; however, the rates in most published studies of infant siblings have been significantly higher (e.g., Landa & Garrett-Mayer, 2006). Zwaigenbaum et al. (2005) have followed a sample of 150 infant siblings of children with autism and 75 low-risk infants from the age of 6 months or younger. Because children were enrolled prior to onset of symptoms, the sample was based on risk for developing symptoms rather than parental concern about symptoms. Zwaigenbaum et al. (2005) reported on a sample of 65 high-risk and 23 low-risk siblings that had been followed up to at least 24 months. Infants were assessed using the Autism Observation Scale for Infants (AOSI; Bryson, McDermott, Rombough, Brian, & Zwaigenbaum, 2007), which measures visual attention, response to name, response to a brief still face, anticipatory responses, imitation, social babbling, eye contact and social smiling, reactivity, affect, ease of transitioning, and atypical motor and sensory behaviors. These markers did not distinguish groups at 6 months of age on the basis of their diagnostic classification at 24 months; however, a subset of the children who were later diagnosed exhibited impairments in responding to name or unusual sensory behaviors. By 12 months groups could be distinguished on the basis of having at least seven markers. Only 2 of 58 at risk siblings who did not receive an ASD diagnosis and none of the 23 controls exhibited seven or more markers. Predictive 12-month markers from the AOSI included atypical eye contact, visual tracking,

disengaging visual attention, orienting to name, imitation, social smiling, reactivity, social interest, and sensory-oriented behaviors. Parents of children who received an ASD diagnosis at 24 months also reported poor gesture use and understanding of words (Mitchell et al., 2006).

Two risk behaviors that were not as well documented in retrospective home videotape studies were identified in the prospective study by Zwaigenbaum et al. (2005). First, differences in visual attention that emerged between 6 and 12 months were observed in infants who later developed ASD. Such infants showed a decline in their performance on a visual attention task that required the infant to disengage his/her attention from a previously salient stimulus; in contrast, none of the infants whose performance was similar or better at 12 months relative to their performance at 6 months developed ASD. Second, infants who later developed ASD exhibited differences in temperament characterized by a lower activity level and more frequent and intense distress reactions. They also spent longer fixating on a single object and were less active in their spontaneous visual exploration. Detailed study of the first nine children who developed ASD (Bryson, Zwaigenbaum, et al., 2007) revealed two subgroups based on the presence or absence of cognitive decline between 12 and 24 months. In children with cognitive loss, symptoms emerged earlier or were more severe. Several investigators have now documented a pattern of cognitive and behavioral decline in infants who develop ASD (reviewed in Dawson et al., 2006).

Landa and Garrett-Mayer (2006) reported a prospective, longitudinal study that described the cognitive development of high-risk infant siblings who later developed ASD, in comparison to high-risk infant siblings who later developed language delay without autism, and unaffected infants. Infants did not differ at 6 months, but by 14 months, the children who developed ASD differed from the unaffected group in gross and fine motor, receptive and expressive language, and overall intelligence on the Mullen scales (Mullen, 1995). Landa, Holman, and Garrett-Mayer (2007) recently described patterns of development from 14 to 24 months in children with early and later diagnosis of ASD. They found that the early-diagnosis group differed from later diagnosis children,

siblings with broader phenotype, and nonrisk control infants in their social, communication, and play behavior. For the early-diagnosis group, growth trajectories suggested that autism may involve developmental arrest, slowing, or even regression.

Retrospective and prospective behavioral studies have led to the development of assessment measures of autism risk behaviors that can be administered to infants (Bryson, McDermott, et al., 2007). The Autism Observation Scale for Infants was developed by Zwaigenbaum and colleagues (2005). This scale involves assessment of 18 risk markers for autism within a brief observational assessment. Infants are engaged in semistructured play and systematic presses are designed to assess various target behaviors, including visual tracking, and attentional disengagement, coordination of eye gaze and action, imitation, affective responses, early social–communicative behaviors, behavioral reactivity, and sensory–motor development. The First Year Inventory (Watson et al., 2007) is a parent questionnaire designed to assess behavioral symptoms related to autism in 12-month-olds. Similar to the Modified-Checklist for Autism in Toddlers (Robins, Fein, Barton, & Greene, 2001), which was developed for children 18–24 months of age, the First Year Inventory is designed to be a screening instrument for autism that can eventually be readily used by pediatricians and other primary health care providers. Validity, sensitivity, and specificity data on these instruments are promising.

Neurophysiological risk indices

New approaches to early detection of infants at risk for ASD are focusing on neurophysiological risk indices (endophenotypes) with the hope that such measures will improve our ability to identify infants who will develop ASD. The identification of endophenotypes, intermediate, quantifiable traits that predict an individual's risk of having a disorder, which can be linked to underlying cause (Castellanos & Tannock, 2002), will accelerate progress in both clinical and basic research. Endophenotypes based on neurobiological markers (Dawson, Webb, et al., 2002; Skuse, 2000) are likely to be especially useful. In other infant risk populations, neurophysiological

measures are more sensitive than behavioral measures at detecting infants who developed later developmental problems (e.g., Black, deRegnier, Long, Georgieff, & Nelson, 2004; Hood & Atkinson, 1990). In a 6-year longitudinal study of maternal depression involving 160 mother–infant pairs, Dawson et al. (Dawson et al., 1999; Dawson, Frey, Panagiotides, Osterling, & Hessl, 1997) found that infants of depressed mothers showed atypical EEG responses in social situations (e.g., playing with mother or an experimenter); these EEG patterns predicted later presence of behavioral and emotional problems.

Event-related potentials (ERPs) to faces. Given the core impairment in social relatedness found in ASD, neurophysiological measures that assess early social brain circuitry might be sensitive indices of risk for ASD. Dawson and Webb have been interested in face processing ability as a potential neural trait marker for susceptibility to ASD. An innate potential for cortical specialization for faces has been proposed, with experience with faces being necessary and driving such specialization (Johnson, 2005; Nelson, 2001). Experience with faces in the first year of life can influence the development of face perception abilities (e.g., Le Grand, Mondloch, Maurer, & Brent, 2001; Pascalis et al., 2005). Typical 6- to 7-month-old infants reliably exhibit different ERPs to familiar versus unfamiliar faces and to different emotional expressions (de Haan & Nelson, 1997; Nelson & De Haan, 1996).

Behavioral and neuroimaging studies have found consistent evidence for face processing impairments in individuals with ASD (Boucher & Lewis, 1992; Boucher, Lewis, & Collis, 1998; Gepner, de Gelder, & de Schonen, 1996; Klin et al., 1999). Functional magnetic resonance imaging (fMRI) studies conducted with typical individuals indicate that the right fusiform gyrus is more activated during perception of faces than nonface stimuli (e.g., Haxby et al., 1994, 1999; Kanwisher, McDermott, & Chun, 1997). Individuals with ASD exhibit irregular and inconsistent patterns of fusiform gyrus activation; some studies have found that areas involved in object processing are activated instead (Pierce, Muller, Ambrose, Allen, & Courchesne, 2001; Schultz et al., 2000).

Preschool-aged children with ASD fail to show different ERPs to familiar versus unfamiliar faces (Dawson, Carver, et al., 2002), faces versus objects (Webb, Dawson, Bernier, & Panagiotides, 2006), and fearful versus neutral faces (Dawson, Webb, Carver, Panagiotides, & McPartland, 2004), whereas mental age-matched children with idiopathic developmental delay and typical development (Dawson, Carver, et al., 2002) do show such differences. Adolescents and adults with ASD (McPartland, Dawson, Webb, & Panagiotides, 2004) as well as parents of children with ASD also show a similar atypical ERP to faces (Dawson et al., 2005) and facial expressions (Dawson, Webb, Estes, Munson, & Faja, 2008), suggesting that this electrophysiological endophenotype might be a neural trait marker for autism genetic susceptibility. Given that typically developing infants as young as 6 months of age show different ERPs to familiar versus unfamiliar faces (De Haan & Nelson, 1997; Webb, Long, & Nelson, 2005), and to facial expression of emotion (Nelson & De Haan, 1996), ERP measures are currently being investigated as an early index of risk for ASD in infants. Promising evidence for this approach comes from a recent study of infant siblings by Carver et al. (McCleery, Burner, Dobkins, & Carver, 2006). They found that, in contrast to nonrisk infants, infant siblings failed to show different ERP responses to faces versus objects.

Based on the idea that face-processing impairments in individuals with ASD may arise from abnormal development of a subcortical system involved in face processing that originates in the magnocellular pathway of the visual system, McCleery, Allman, Carver, and Dobkins (2007) measured the sensitivity of the magnocellular pathway in infant siblings of children with autism and low-risk control infants. They used a visual stimulus designed to selectively stimulate the magnocellular pathway (sensitivity to luminance) and found that high-risk infants exhibited sensitivities nearly twofold greater than those of control infants. Although this study showed enhanced (rather than reduced) luminance sensitivity in high-risk infants, the authors argue that this still should be considered to reflect an abnormality of the magnocellular pathway. They further argue that such an abnormality might contribute to the face-processing impairments found in autism. They note that the magnocellular pathway,

via the superior colliculus, provides it to the amygdala, which in turn, is involved in rapid subcortical processing of faces. This methodology may eventually be useful in assessing very young infants at risk for ASD.

ERPs to speech sounds. Another promising neurophysiological index of risk for ASD is ERPs to speech sounds. Research suggests that young children with ASD have atypical ERPs to speech, which is correlated with their preference for listening to speech sounds. In a sample of 3- to 4-year-old children with ASD, Kuhl, Coffey-Corina, Padden, and Dawson (2004) found that listening preferences in children with ASD differed dramatically from those of typically developing children. Children with ASD preferred listening to mechanical-sounding auditory signals (signals acoustically matched to speech and referred to as "sine-wave analogs") rather than speech (motherese). The preference for the mechanical-sounding auditory signal was significantly correlated with lower language ability, more severe autism symptoms, and abnormal ERPs to speech sounds. Children with ASD who preferred motherese were more likely to show different ERPs (mismatch negativity) to different phonemes, whereas those who preferred the mechanical-sounding auditory signal showed no differences between ERP waveforms in response to two different syllables. Such ERP measures are currently being studied in infants at risk for ASD to determine whether they are predictive of later ASD and/or language impairment.

In addition to early indices of brain function, structural and chemical brain imaging measures offer another way of assessing risk for ASD. In the next section, studies using such measures during the infant–preschool period are described.

Atypical brain growth

An atypical trajectory of head growth in the first 2 years of life appears to be a phenotypic risk index in ASD (Courchesne & Pierce, 2005; Redcay & Courchesne, 2005). The pattern of growth in head circumference (HC) in ASD is characterized by normal head size at birth followed by an accelerated pattern of growth in HC that appears to begin at about 4 months of age (Dawson et al., 2007; Gillberg & de Souza,

2002; Hazlett et al., 2005; Webb et al., in press). Courchesne and colleagues (Courchesne, Carper, & Akshoomoff, 2003) reported an increase in HC of 1.67 *SD* between birth and 6–14 months. In a meta-analysis using HC (converted to brain volume), brain volume measured from MRI, and brain weight from autopsy studies, Redcay and Courchesne (2005) found that brain size changes from 13% smaller than controls at birth to 10% greater than controls at 1 year, and only 2% greater by adolescence.

Dawson et al. (2007) examined HC growth longitudinally in 28 children with ASD spectrum disorder from birth through 36 months of age, replicating earlier findings of accelerated head growth. Pattern of head growth was not found to vary as a function of subtype of ASD (autism vs. pervasive development disorder, not otherwise specified) or history of autistic regression (Webb, Munson, Brock, Abbott, & Dawson, in press). Children with ASD, on average, did not have significantly larger HC at birth; however, by 1 year of age, HC was nearly 1 standard deviation larger than the national CDC norms. This unusual and rapid increase in head growth from birth to 12 months was reflected in a significant difference in slope in HC Z scores during this period. Of interest, although children's HC was larger than normal by 12 months of age, the rate of growth in HC after 12 months was not significantly different than the normative sample. Thus, the rate of HC growth appears to decelerate in infants with ASD after 12 months of age relative to the rate from birth to 12 months of age, suggesting that the early period of exceptionally rapid head growth is restricted to the first year of life.

The period of accelerated head growth slightly precedes and then overlaps with the onset of noticeable behavioral risk indices. Notably, the period after 12 months of age, during which deceleration of rate of head growth was detected, is associated with a slowing in acquisition or actual loss in skills in infants who develop ASD (Dawson et al., 2007). In sample of infant siblings of children with ASD, the pattern of rapid growth from birth to 12 months followed by deceleration after 12 months was found to be a risk marker for developing autism symptoms by 24 months of age (Elder, Dawson, Toth, Munson, & Fernandez-Teruel, 2008).

Structural brain imaging

Results from structural MRI studies are consistent with the results of HC studies. Sparks et al. (2002) found that 3- to 4-year-olds with ASD have significantly larger total cerebral volume compared with age-matched typically developing children and age- and IQ-matched developmentally delayed children. In another study of 2- to 4-year-olds with ASD, 90% of children with ASD were found to have MRI-based brain volumes larger than normal (Courchesne et al., 2001). This abnormal brain growth appears to be due primarily to excessive enlargement cerebral white matter and cerebral grey matter. Courchesne et al. (2001) suggested that, early on, children with ASD show an anterior–posterior gradient of overgrowth, with the frontal lobe being the largest, although this needs further confirmation.

Sparks et al. reported that the amygdala was proportionally enlarged relative to total cerebral volume, especially in children with more severe symptoms. Enlarged amygdala at age 3 years (but not total cerebral volume) predicted a more severe course from 3 to 6 years of age (Munson et al., 2006). Autopsy studies of ASD (Pickett & London, 2005) have documented cellular abnormalities of the amygdala including reduced numbers of neurons (Schumann & Amaral, 2006), or reduced cell size and increased neuronal cell packing density (Bauman & Kemper, 1985, 2005). Schumann and Amaral (2006) have identified the lateral nucleus as having accentuated pathological features.

Chemical brain imaging

Magnetic resonance spectroscopy imaging (^{1}H-MRSI) provides a noninvasive method for characterizing tissue-based chemistry and cellular features in vivo. Although MRI is sensitive to changes in tissue water characteristics and defining structure at a macroscopic level, it is insensitive to much of cellular level organization. In this regard,[1] H-MRS has been used to detect abnormalities in brain regions that appear normal in MRI, as well as shed light on pathology underlying MRI-visible abnormalities. Several chemicals can be measured as spectral peaks,

including N-acetyl aspartate (NAA), creatine, choline, and myoinositol. Glutamate and glutamine are typically reported as combined peaks. NAA appears to be a sensitive marker for neuronal integrity or neuronal-glial homeostasis.

An MRSI study of 3- to 4-year-old children with ASD conducted by Friedman et al. (2003) revealed regional and global decreases in NAA as well as lower levels of other chemicals and prolonged chemical T2 relaxation times. Analyses further demonstrated a predominately gray matter tissue distribution of these chemical abnormalities (Friedman et al., 2006). These findings have implications for understanding the mechanism for abnormal brain growth in ASD. One hypothesis is that enlarged brain volume in ASD is related to a failure of apoptosis or synaptic pruning. This hypothesis would predict increased NAA concentrations, reflecting increased or more densely packed neurons or increased synaptic connections. Findings were, however, decreased NAA concentrations and prolonged chemical and water T2 in the 3- to 4-year-old ASD group (Friedman et al., 2003). These MSRI findings suggest a pattern of cellular alterations, predominantly affecting gray matter at an early age, that may reflect reduced synapse density perhaps secondary to migratory/apoptotic abnormalities (Fatemi & Halt, 2001), column density/packing abnormalities (Casanova, 2004) and/or active processes such as reactive gliosis and edema (Vargas et al., 2005).

To assess whether measures of structural and chemical brain development can serve as risk indices for ASD, a large collaborative infant sibling brain imaging project involving University of Alberta, University of North Carolina, McGill University, University of Washington, Washington University at St. Louis, and Yale University was recently funded as part of the National Institutes of Health Autism Centers of Excellence Program.

Summary

Progress is being made in identifying genetic and environmental factors that contribute to susceptibility for ASD. Phenotypic risk indices for ASD that can be measured in the first year of life include several behavioral risk indices, with the earliest symptoms being failure to respond to name, abnormal visual attention, and temperamental difficulties. Future studies of early brain development, as measured by neurophysiological responses, such as ERPs to faces and speech sounds, HC trajectory, and structural and chemical brain imaging techniques, will evaluate the usefulness of these measures for early detection of risk for ASD. Collaborative studies that follow large samples of infant siblings of children with autism to document the relation between the emergence of symptoms and early functional, structural, and chemical alterations in brain development offer promise of identifying neural mechanisms that account for ASD, as well as brain-based methods for detection of infants at high risk for developing ASD before the full blown syndrome is manifest.

ASD clearly is not a static brain disorder but rather is characterized by dynamic postnatal changes in the brain and behavior. According to a cumulative risk model, an accumulation of early risk factors lowers the threshold of vulnerability of suboptimal neuronal processes in ASD. It is likely that brain–environment interactions are additional risk processes that contribute to the eventual development of ASD. Environmental contributions to risk processes can include both biological (e.g., inflammation) and experiential factors (altered patterns of social interaction). The next section provides a discussion of how early experiential factors, namely, altered patterns of interaction between the child and his or her social environment, represents one type of risk process associated with the development of ASD.

Early Experience as a Risk Process in the Development of ASD

The social motivation hypothesis

Impairments in social orienting, joint attention, responses to emotions, imitation, and face processing are evident by toddlerhood or preschool age in ASD. To help understand this wide range of impairments, all of which involve reduced engagement with the social world, Dawson and others have proposed the *social motivation hypothesis* (see Figure 2). This hypothesis posits

that some of the social impairments evident in ASD, such as the well-documented impairments in face processing, are not fundamental, but rather are secondary to a primary impairment in social motivation, which results in failure to attend to and affective tag socially relevant stimuli (Dawson, Webb, Wijsma, et al., 2005; Dawson, Carver, et al., 2002; Grelotti, Gauthier, & Schultz, 2002; Waterhouse, Fein, & Modahl, 1996).

Evidence supporting a core impairment in social motivation comes from both clinical and observational studies. One of the earliest indicators of reduced social motivation is a lack of "social orienting" (Dawson et al., 2004; Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998). Diagnostic criteria describe "a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people" and "lack of social or emotional reciprocity." Preschool age children with ASD are less likely to smile when looking at their mothers during social interaction (Dawson, Hill, Galpert, Spencer, & Watson, 1990), especially during joint attention episodes (Kasari, Sigman, Mundy, & Yirmiya, 1990). Young children with ASD fail to show normal preferences for speech sounds (Klin, 1991, 1992; Kuhl et al., 2004). Sung et al. (2005) found evidence that a social motivation trait (e.g., seeking social activities and friendships) was heritable in multiplex autism families.

According to the social motivation hypothesis, because of reduced social motivation, the infant at risk for ASD spends less time spent paying attention to and socially engaged with people. The infant at risk for ASD, instead, has a stronger focus on objects (Zwaigenbaum et al., 2005). Reduced engagement with the social world contributes to a failure to develop expertise in face, language, and other aspects of processing of social information (Dawson, Webb, & McPartland, 2005; Dawson, Webb, Wijsman, et al., 2005; Grelotti et al., 2002). Because experience drives cortical specialization (Nelson, 2001), reduced attention to people, including their faces, gestures, and speech, also results in a failure of specialization and less efficient function of brain regions that mediate social cognition (e.g., prolonged latency in electrical brain responses to face stimuli; McPartland et al., 2004). In an ERP study of preschool aged children with ASD, Webb et al. (2006) found that ERPs to faces were not only slower, but also more diffusely distributed across the scalp, whereas typical children showed a well-localized right temporal ERP (N170) to faces.

The abnormal trajectory for brain development in ASD cannot be explained by a lack of exposure to people. Parents of infants with ASD, like those of typically developing infants, hold, talk to, and interact with their infant. If such interactions are not inherently interesting or rewarding for the infant, however, s/he might not be actively attending to the face and voice, tagging such information as emotionally relevant, or perceiving the social information within a larger social/affective context. Recent research by Kuhl and colleagues (Kuhl, 2007; Kuhl, Tsao, & Liu, 2003) suggests that simple exposure to language does not necessarily facilitate the development of brain circuitry specialized for speech perception. Instead, speech needs to be experienced by the infant within a social interactive context for speech perception to develop normally.

Social motivation impairments in autism might be related to a difficulty in forming and generalizing representations of the reward value of social stimuli (Dawson, Carver, et al., 2002). One of the primary neural systems involved in processing reward information is the dopamine system (Schultz, 1998). Dopaminergic projections to the striatum and frontal cortex, particularly the orbitofrontal cortex, mediate the effects of reward on approach behavior. Formation of representations of reward value in the orbitofrontal cortex relies on input from basolateral amygdala (Schoenbaum, Setlow, Saddoris, & Gallagher, 2003). The amygdala is implicated in both the focusing of attention of emotionally relevant stimuli and the learning and consolidation of emotional memories (LaBar, 2007). This dopamine reward system activates in response to social engagement, for example, when making eye contact (Kampe, Frith, Dolan, & Frith, 2001). Dopamine D2 receptors in the nucleus accumbens have been shown to be involved in social attachment (Gingrich, Liu, Cascio, Wang, & Insel, 2000). In young children with ASD, the severity of joint attention impairments is strongly correlated with performance on tasks tapping the medial temporal lobe–orbitofrontal circuit (e.g., delayed nonmatching to sample,

object discrimination reversal; Dawson, Munson, et al., 2002).

Oxytocin and vasopressin promote a wide range of social behaviors, including social affiliation (Witt, Winslow, & Insel, 1992), maternal behavior (Pedersen, Caldwell, Walker, Ayers, & Mason, 1994), and social attachment (Insel & Hulihan, 1995; Winslow, Hasting, Carter, Harbaugh, & Insel, 1993). These peptides operate on social behavior through their influence on the mesocorticolimbic dopamine circuit. A circuit linking the anterior hypothalamus to the ventral tegmental area and the nucleus accumbens may mediate reward sensitivity in the context of social interaction (Insel & Fernald; 2004). Modahl et al. (1998) reported that plasma concentration of oxytocin is reduced in children with autism. Kim et al. (2002) found nominally significant transmission disequilibrium between an arginine vasopressin receptor 1A (AVPR1A) microsatellite and autism. AVPR1A is a V_{1a} receptor in the brain that has been shown to mediate action of vasopressin. Studies have also found an association of the oxytocin receptor gene and autism (Jacob et al., 2007; Wu et al., 2005). Recent psychopharmacological studies have demonstrated that intravenous oxytocin administration reduces repetitive behavior (Hollander et al., 2003) and increases comprehension of affective meaning (Hollander et al., 2007) in individuals with ASD.

Given that altered early experience may act as risk processes in the development of ASD, the goal of intervention is to target these risk processes to provide a more enriched environment for the at-risk child. Animal studies have demonstrated that early enrichment can mitigate the effects of genetic and environmental risk factors. These studies will be reviewed next.

Animal Studies Demonstrating the Effects of Early Enrichment

A large body of research has demonstrated the effects of environmental enrichment on brain and behavioral development in animals. As early as 1947, Hebb demonstrated improved memory of rats that were allowed to freely explore his house compared with caged rats. Environmental enrichment has been shown to direct affect brain

development and neural plasticity in animals, as measured by the weight and thickness of the cortex, the density or affinity of neurotransmitter receptors, and increased numbers of synapses and density of dendritic branching (Bredy, Humpartzoomian, Cain, & Meaney, 2003; Diamond, Rosenzweig, Bennett, Linder, & Lyon, 1972). Changes at the synapse as well as increases in the number of neurons in regions such as the hippocampus have been induced in adult animals (Greenough, Volkmar, & Juraska, 1973; Kempermann, Kuhn, & Gage, 1997). Enrichment also results in molecular changes, including modulation of the genetic expression of neurotransmitter pathways, differential transcription of neurotransmitter-related target genes, and increased neurotrophic factors (Pham, Winblad, Granholm, & Mohammed, 2002; Rampon et al., 2000). Long-term potentiation of synapses, believed to be a cellular representation of memory, via increased excitatory responses results from enrichment (e.g., Foster, Gagne, & Massicotte, 1996). In adult primates, increased density of dendritic spines in the hippocampus and prefrontal cortex were found following 1 month of enrichment (Kozorovitskiy et al., 2005). Environmental enrichment results in improved learning and memory, increased exploration, more rapid habituation, and decreased fearful responding to novelty (e.g., Benaroya-Milshtein et al., 2004; Duffy, Craddock, Abel, & Nguyen, 2001; Escorihuela, Tobena, & Fernandez-Teruel, 1995; Schrijver, Bahr, Weiss, & Wurbel, 2002; Wong & Jamieson, 1968). In contrast, environmental deprivation in primates results in cognitive impairments and differences in brain structure (e.g., Floeter & Greenough, 1979; Sackett, 1972).

Animal models of developmental and degenerative disorders have demonstrated the role of early enrichment in mitigating the effects of genetic risk and injury. Such animal studies have varied living conditions, environmental complexity or novelty, and level of sensory, cognitive, motor, or social stimulation to demonstrate how experience can influence brain development and diminish the effects of genetic risk and/or injury (for reviews, see Lewis, 2004; Nithianantharajah & Hannan, 2006). Enrichment offsets the effects of earlier environmental stressors such as reduction of exaggerated stress responses in prematurely weaned pups (Bredy

et al., 2003; Francis, Diorio, Plotsky, & Meany, 2002). Enrichment following frontal lobe lesions results in behavioral and anatomical improvements (Hamm, Temple, O'Dell, Pike, & Lyeth, 1996; Kolb & Gibb, 1991). Enrichment in the form of social and physical stimulation influences recovery following infarct and protect against drug-induced seizures (Faverjon et al., 2002; Johansson & Ohlsson, 1996; Young, Lawlor, Leone, Dragunow, & During, 1999).

Animal models of genetic diseases have demonstrated that enrichment can reduce or delay the onset of the motor impairments associated with both cerebellar degeneration (the *lurcher* mutation) and Huntington disease (an autosomal dominant disorder; Caston et al., 1999; Glass, van Dellen, Blakemore, Hannan, & Faull, 2004). *Fmr1*-KO mice are commonly used to model fragile X. These mice exhibit cognitive and brain anomalies associated with fragile X; enrichment, however, influences exploratory behavior, dendritic branching, the number of dendritic spines, and expression of glutamate signaling, but does not appear to directly impact the protein implicated in the genetic mutation (Restivo et al., 2005).

As a result of standard housing conditions, deer mice develop restricted, repetitive motor behaviors, similar to those seen in individuals with ASD. Mice exposed to enriched rather than standard environments early in their development do not develop motor stereotypies, whereas mice exposed later in development do (e.g., Powell, Newman, McDonald, Bugenhagen, & Lewis, 2000; Turner, Lewis, & King, 2003; Turner, Yang, & Lewis, 2002). Thus, there appears to be a critical period during which environmental enrichment precludes the development of these behaviors in mice. Furthermore, mice that did not exhibit stereotyped behavior showed several brain changes, including increased oxidative energy metabolism in the motor cortex, basal ganglia, hippocampus, and amygdala, increased dendritic spine density in the motor cortex and basal ganglia, and more brain derived neurotrophic factor expression. Finally, a rat model of autism has been created via exposure to valproic acid on gestation day 12.5 (Rodier, Ingram, Tisdale, & Croog, 1997). Enrichment reversed most behaviors associated with exposure to valproic acid,

including the frequency of social behavior and latency to social exploration, sensitivity to sensory input, and anxious behavior during learning tasks (Schneider, Turczak, & Przewlocki, 2006).

Taken together, this body of work demonstrates enrichment can mitigate the effects of genetic and environmental risk factors on brain and behavioral development. This raises the possibility that early interventions aimed at stimulating young infants and toddlers at risk for ASD can substantially change the course of both behavioral and brain development. Presumably, according to the social motivation model, this would occur by enhancing social motivation by either stimulating nascent neural circuitry involved in social reward, or by coopting neural reward systems that target nonsocial stimuli through classical conditioning (nonsocial reward, such as a toy, being paired consistently with a social stimulus, such as a person, in the context of treatment; Dawson & Zanolli, 2003). Next, a brief review of approaches to early interventions for infants at risk for ASD will be provided.

Infant–Toddler Interventions Designed to Prevent or Reduce Autism Symptoms

Early intensive behavioral intervention in young children with ASD

Studies of early intensive behavioral intervention demonstrate that early intensive behavioral intervention initiated at preschool age and sustained for 2–3 years results in substantial improvements for a large subset of children with ASD. Gains are found in IQ, language, and educational placement (Birnbrauer & Leach, 1993; Cohen, Amerine-Dickens, & Smith, 2006; Dawson & Osterling, 1997; Fenske, Zalenski, Krantz, & McClannahan, 1985; Harris, Handleman, Gordon, Kristoff, & Fuentes, 1991; Howard et al., 2005; Lovaas, 1987; McEachin et al., 1993; Rogers, 1998; Sallows & Graupner, 2005; Sheinkopf & Siegel, 1998; Smith, Groen, & Wynn, 2000). Common features of successful early intensive behavioral intervention are (a) a comprehensive curriculum focusing on imitation, language, toy play, social interaction, motor, and adaptive behavior; (b)

sensitivity to developmental sequence; (c) supportive, empirically validated teaching strategies (applied behavior analysis); (d) behavioral strategies for reducing interfering behaviors; (e) involvement of parents; (f) gradual transition to more naturalistic environments; (g) highly trained staff; (h) supervisory and review mechanisms; (i) intensive delivery of treatment (25 hr/week for at least 2 years); and (j) initiation by 2–4 years (Dawson and Osterling, 1997; Green, Brennan, & Fein, 2002; National Research Council, 2001; Rogers, 1998). When these features are present, results are remarkable for up to 50% of children. Three randomized controlled trials have assessed the efficacy of comprehensive interventions delivered for 20 or more hours per week. Jocelyn, Casiro, Beattie, Bow, and Kneisz (1998) randomized 35 preschool aged children to an experimental group versus a control group. The experimental group received developmentally based intervention focused on social and communication skills and applied behavior analysis for behavior problems delivered by specially trained day care workers and parents. After 3 months, the experimental group demonstrated significantly increased language performance, but no difference in autism severity, compared with controls. Smith et al. (2000) randomized 28 children with ASD to an experimental group versus a parent training group. The experimental group received extensive parent training and Lovaas' (1987) comprehensive intervention approach for an average of 25 hr per week, delivered in their homes by trained and supervised therapy assistants. The comparison group received parent training, several hours of in home therapy per week for the first few months of the study, and community services. Results after 2 years revealed significant differences in IQ (gain of 15 points in the experimental group vs. loss of 1 point in the control group). Sallows and Graupner (2005) randomized 24 children with autism to a "clinic-directed" group that replicated the intervention provided in Lovaas' original study versus a "parent-directed group" that received intensive hours of treatment but less supervision. After 4 years of treatment, both groups show similar gains in cognitive, language, social, and academic skills. In each group, 48% of children showed rapid learning, achieved IQs and language abilities in the average range, and were

placed successfully in a regular education classroom by age 7.

Interventions for infants and toddlers with ASD

With the goal of intervening at the point when symptoms are first detected, intervention approaches for infants and toddlers with ASD are being developed (Chandler, Christie, Newson, & Prevezer, 2002; Drew et al., 2002; Green et al., 2002; Mahoney & Perales, 2003; McGee et al., 1999). No published randomized studies of infant–toddler interventions have been published yet. Dawson and Rogers have been developing the Early Start Denver Model, which is based on the Denver Model. The Denver Model is a comprehensive intensive early behavioral intervention for preschool-age children with ASD originally developed and evaluated by Rogers and colleagues (Rogers, Hall, Osaki, Reaven, & Herbison, 2000; Rogers, Herbison, Lewis, Pantone, & Reis, 1986; Rogers & Lewis, 1989). The Early Start Denver Model (Smith, Rogers, & Dawson, 2008) is designed to address the unique needs of infant and toddlers with ASD as young as 12 months. Early Start incorporates applied behavior analysis techniques that have received empirical support for improving skill acquisition in very young children with ASD (e.g., Green et al., 2002; McGee et al., 1999), but is delivered in a naturalistic, socially and affectively based relationship context. The intervention is provided in a toddler's natural environment, typically the home, within the context of family and therapist–child interactions. As children reach preschool age, play dates that facilitate child–child interaction and collaboration with preschools are incorporated. In 2003, Dawson, in collaboration with Rogers, initiated a National Institute of Mental Health-funded randomized controlled trial of the Early Start Denver Model with toddlers with ASD at 7the University of Washington. Building on the work of Rogers, the University of Washington project involved developing, refining, and testing both the therapist-training procedures and the toddler intervention model, including a treatment manual, curriculum, and fidelity measures.

Forty-eight toddlers with ASD were randomized to one of two groups: one receives

25–30 hr weekly of the Early Start Denver Model intervention for 2 years; the other, a community comparison group, receives standard community-based interventions provided in the greater Seattle region. The effects of the early intervention are predicted to be partially mediated by the quality of parent–child interaction. Parent–child interaction is viewed as a final common pathway that is influenced both by improvements in parental sensitivity and improvements in child behavior.

Integrating biological measures into the design of an early intervention study for ASD

A goal for the future is to demonstrate that early intervention can have an impact on brain function and organization. Thus, it will be important to incorporate brain-based measures of outcome into intervention and prevention studies. In the current randomized early intervention trial for toddlers with ASD, we hope to demonstrate that very early intervention results not only in significant improvements in behavior, including reduced autism symptoms and increased cognitive, language, and social abilities, but also significant changes in brain function, as reflected in neural responses to social and linguistic stimuli. Both before and after treatment, ERPs to faces and speech stimuli are being collected to assess whether the intervention influences the children's ERP responses to faces versus objects and to speech sounds. Influences on cortical organization and specialization will be assessed by examining the scalp distribution of the ERP.

Outcome measures also include EEG coherence. Functional connectivity in brain networks can be measured by EEG coherence, which assesses the statistical relationships among separate neurophysiological signals measured from the scalp. High coherence between two EEG signals reflects synchronized neuronal oscillations suggesting functional integration between neural populations, whereas low coherence suggests independently active populations. EEG coherence is believed to reflect functional cortical connectivity either directly via corticocortical fiber systems or indirectly through networks that include subcortical structures. In humans, the development of EEG coherence from birth into adulthood has been extensively documented by Thatcher and colleagues (Thatcher, 1994; Thatcher, Krause, & Hrybyk, 1986; Thatcher, Walker, & Guidice, 1987).

EEG coherence is of theoretical relevance to ASD because, as described above (see Figure 2), ASD is associated with abnormalities in connections among distributed neural systems. Impairments in complex behaviors that emerge between 6 and 12 months in ASD, such as joint attention and imitation, are hypothesized to reflect a failure of integration of cortical–cortical and subcortical–cortical systems. Empirical support for reduced connectivity in ASD comes from findings of increased cell dispersion and reduced sizes of cortical minicolumns in brains of individuals with autism (Casanova, Buxhoeveden, Switala, & Roy, 2002) and fMRI studies showing reduced functional connectivity during complex tasks (Just, Cherkassky, Keller, & Minshew, 2004). Based on his neuropathology studies, Casonova et al. (2002) has argued that autism is associated with disruptions among local and global cortical circuits (also see Belmonte et al., 2004; Courchesne & Pierce, 2005; Rippon, Brock, Brown, & Boucher, in press). Murias et al. conducted a study showing reduced EEG coherence in adults with ASD (Murias, Webb, Greenson, & Dawson, 2008). They examined coherent oscillatory activity between all pairs of electrodes in a high-density electrode array in the spontaneous EEG of 18 adults with ASD and 18 control adults at quiet rest. They found robust contrasting patterns of over- and underconnectivity at distinct spatial and temporal scales. In the delta and theta (2–6 Hz) frequency range, individuals with ASD showed locally elevated coherence, especially within left hemisphere temporal and frontal regions. In the lower alpha range (8–10 Hz), the ASD group showed globally reduced EEG coherence within frontal regions, and between frontal and all other scalp regions. The frontal lobe was poorly connected with the rest of the cortex in this frequency range. This is consistent with metabolic studies showing reduced correlated blood flow between frontal and other regions individuals with autism (Horowitz, Rumsey, Grady, & Rappoport, 1988). Measures of EEG coherence will provide insight into the effects of early intervention on functional connectivity in the brain in ASD.

Prevention studies in ASD

To date, no prevention studies have been conducted with infants at risk for ASD. Both the National Institutes of Health, as part of the newly launched National Institutes of Health Autism Centers of Excellence program, and Autism Speaks, in their recent initiative to fund treatment studies targeting infants and toddlers at risk for ASD, have invested considerable funds in new studies aim at treating and preventing ASD. Many of these studies are exploring intervention methods that enhance social motivation and promote early social engagement and reciprocity. Some investigators are incorporating neurophysiological measures in the design of these intervention studies to assess whether interventions initiated before the full syndrome of autism is present can prevent autism and result in normal patterns of brain function and organization.

The role of early parent–child interactions in prevention studies. Many of the interventions that are currently being tested with infants at risk for ASD focus on enhancing parent–infant interactions. The important role of parents as collaborators in and mediators of intervention was first introduced by Eric Schopler in the 1960s. Schopler's visionary notion that parents' ability to participate in intervention by adapting their styles of interaction to promote social interaction and communication continues to influence the field today. It has been demonstrated that parents who display higher levels of synchronization and contingent responses during interaction have children with ASD who develop superior communication skills over periods of 1, 10, and 16 years (Siller & Sigman, 2002). Early nonverbal communication, especially joint attention, is strongly related to language outcome for children with ASD and typical development (Brooks & Meltzoff, 2005; Dawson et al., 2004; Sigman & Ruskin, 1999; Toth, Munson, Meltzoff, & Dawson, 2006). In normal development, as well, language acquisition has been found to depend on social interactions in which the adults' communicative behavior is salient, well timed, and contingent (Bruner, 1983). In a study of 72 young children with ASD, it found that early social attention was related to language ability, and the relation between social attention and child's language ability was fully mediated by the child's ability to share attention with others (Toth et al., 2006).

Very early interventions that target parent–infant interaction are based on the assumption that relationships are transactional; the infant exerts an effect on the parent and influences the sensitivity and quality of the parent response. Parents find it more difficult to respond sensitively to infants who have regulatory difficulties and who have less reciprocal interaction styles (Kelly, Day, & Streissguth, 2000; O'Connor, Sigman, & Brill, 1987; Tronick & Field, 1986; Yehuda et al., 2005). Yirmiya et al. (2006) found that infant siblings are less synchronous with their mothers during interactions and display more neutral affect. By 12 months of age, infants later diagnosed with ASD are less likely to smile, fail to orient to name, have difficulty establishing eye contact, lack communicative vocalizations, are difficult to cuddle, are exceptionally fussy or passive, exhibit sleeping and feeding problems, and are sensitive to noise/touch (Zwaigenbaum et al., 2005). Interventions need to take into account the individual characteristics of both members of the dyad, and be sensitive to the "dance" that the dyad performs together (Poehlmann & Fiese, 2003). In studies of other at-risk infant populations, brief, behaviorally focused interventions have been found to be effective when the target of intervention is parental sensitivity and infant contingent responding. Bakermans-Kranenburg, Van Ijzendoorn, and Juffer (2003) conducted a meta-analysis of 81 studies of at-risk infants that promoted mother–infant interaction and found that interventions focusing on promoting maternal sensitivity were more effective than the combination of all other types of interventions. The most effective interventions for enhancing maternal sensitivity involved fewer than 16 sessions, used video feedback, and were utilized with populations in which child characteristics, rather than parent characteristics, were risk factors. Such approaches might also be effective in infants at risk for ASD. By facilitating early social engagement and reciprocity between the at-risk infant and his/her social partners, it may be possible to prevent ASD in some cases.

Understanding the Variability in Outcome in ASD

Models of prevention and outcome in ASD must explain the substantial variability in response to early intervention that exists. Despite receiving early, high-quality, intensive intervention, some children with ASD nevertheless make very slow progress. A sizable minority of children fails to develop speech and shows significant, enduring cognitive and social impairments. It is likely that prevention studies focused on intervention with infants at risk for ASD also will reveal substantial variability in response to treatment. The tremendous etiological and phenotypic heterogeneity in ASD indicates that ASD is comprised of many subtypes characterized by different genetic etiologies, brain bases, and treatment responses. It is hypothesized that individual differences in outcome can be accounted for by several factors: (a) the nature and severity of the effects of genetic and environmental risk factors on early biological[1] development, which define the range of neural plasticity that is possible; (b) the degree to which such influences negatively alters early interactions between and child and his/her environment, which defines the nature and degree of early stimulation the child will receive; (c) the degree to which early intervention allows the social partner to effectively adapt to the at-risk child's altered manner of interacting with the world in such a way to facilitate normal social and linguistic input to the developing brain; and (d) the timing and intensity of such early intervention. Thus, there is not a one–one correspondence between genetic or environmental factors and the occurrence of ASD. Rather, there are individual differences in the developmental pathway that a given child will follow that can be explained in terms of the interaction between early risk factors and the context in which the child develops. Although change in

the developmental pathway is always possible, canalization also constrains the magnitude and quality of change. Therefore, "the longer an individual continues along a maladaptive ontogenetic pathway, the more difficult it is to reclaim a normal developmental trajectory" (Cicchetti & Cohen, 1995, p. 7). Thus, it is hypothesized that the earlier risk for ASD is detected and intervention can begin, the greater the chance that intervention will alter the abnormal developmental trajectory of individuals with ASD and help guide brain and behavioral development back toward a normal pathway and in some cases, prevent the full syndrome of ASD. Harris and Handleman (2000) found that children who began treatment before age 4 had much better outcomes, and that the younger and older treatment groups were virtually nonoverlapping in their placements in a regular versus special education classroom in elementary school.

Some child variables have been found to predict response to early intervention. Predictive pretreatment child characteristics include frequency of social initiations, level of social avoidance, imitation ability, severity of core autism symptoms, imitation, presence of dysmorphic physical features, pretreatment IQ, level of toy play, and use of language (Ingersoll, Schreibman, & Stahmer, 2001; Rogers, 1998; Sallows & Graupner, 2005; Sherer & Schreibman, 2005). These behaviors can be broadly classified into three categories: (a) *level of social engagement* indexed by infrequent social initiations, social avoidance, poor imitation ability, and social and communicative symptoms; (b) *level of intellectual ability* indexed by low IQ, delayed toy play, and presence of dysmorphology; and (c) *level of prelinguistic/linguistic ability*. This author speculates that these three types of behaviors reflect the presence and severity of three overlapping disorders (a) *core autism*, (b) *comorbid mental retardation*, and (c) *comorbid language impairment*, respectively (see Figure 3). A child who has severe ASD, mineralocorticoid receptor (MR), and language disability is likely to be highly aloof and avoid social interactions, show little exploration of even the nonsocial environment, nonfunctional use of toys, and exhibit little or no vocalizations or sounds. This child is likely to make slow progress despite the best intervention. This is not meant to

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1. It is increasingly recognized that autism affects not only brain development but also other systems, such as gastrointestinal and immune systems (see Herbert et al., 2006). These can be considered another type of risk process that influences the manner in which the child interacts with his or her environment. Addressing these risk processes via medical treatment is also important for optimal outcome.

Early indices of core ASD pertain to social engagement: Social initiation, social approach, and other social behaviors such as social smiling, social orienting, social imitation, shared attention, response to social reinforcers.

Autism

Mental Retardation

Developmental Language Impairment

Early indices of mental retardation pertain to learning ability: IQ, level of toy play and exploration, dysmorphology, seizures, and other indices of rate of learning, such as number of repetitions required for skill acquisition, ability to generalize skills, interfering motor stereotypies, need for highly structured intervention strategies

Early indices of developmental language impairment pertain to vocal-verbal ability: Behaviors include vocalizations, attention to speech sounds, verbal imitation skills, rate of progress in acquiring speech, oral praxis, auditory processing skills, need for visual supports
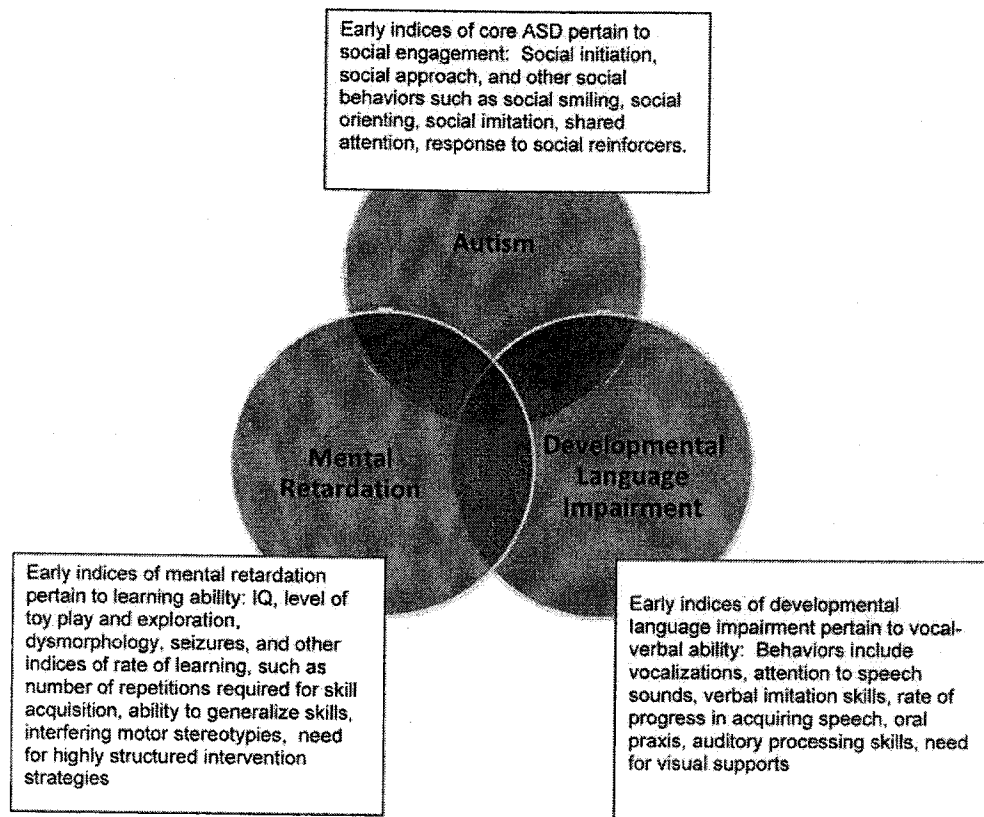
Figure 3. The response to intervention in autism spectrum disorder (ASD) is the predicted severity of ASD and presence/absence of two highly comorbid disorders: mental retardation and developmental language impairment. [A color version of this figure can be viewed online at journals.cambridge.org/dpp]

minimize the importance of this progress for quality of life and functional skills for such individuals, however. For the severely affected child, intervention can promote functional communication and adaptive behaviors, reduce maladaptive behaviors, and lead to a more fulfilling, less restrictive life.

In contrast, a child with mild ASD, mild or no MR, and mild or no language disability initially might not exhibit joint attention, engage in reciprocal play, or have an interest in others, and likely will engages in repetitive, unimaginative toy play. This child, however, is likely to show or quickly develop an interest in predictable social routines, enjoy rough and tumble play, respond well to at least some social reinforcers, explore at least a limited number of toys, experiment with cause and effect, and exhibit self-directed vocalizations or speech. This child, whose diffi-

culties are mild and primarily manifest in the social–communicative domain, has a much higher likelihood of responding very well to early intervention. Specific assessment for comorbid mental retardation and language impairment (which can be manifest in a number of ways, including developmental receptive aphasia, oral dyspraxia, and so on) may allow improved prediction of response to early intervention and led to more individually tailored treatment approaches.

In addition to behavioral predictors of response to treatment, a goal is to identify genetic and other biological predictors. In the randomized trial of early intensive intervention for toddlers at the University of Washington, all children undergo brain imaging studies before entering into treatment. Both structural and chemical brain measures are being investigated as potential moderators of response to early intervention. Variation

in response to intervention may be a useful way to examine genetic heterogeneity in ASD. A better understanding of the variability in response to treatment in ASD can provide insight into medical treatments that may help children who are making slower progress in response to behavioral interventions.

Conclusion

This article concentrated on early intensive behavioral interventions as a means of preventing and treating autism. An equally important goal is to prevent and treat core ASD symptoms by eliminating or mitigating the detrimental effects of genetic and environmental risk factors on biological and behavioral development in autism. This goal is particularly important for the large number of individuals who experience severe behavioral and cognitive challenges despite having access to high-quality early intensive behavioral intervention. By integrating biological processes into the design and evaluations of interventions for children with ASD, a more comprehensive understanding of the mechanisms responsible for effective intervention will be possible (Cicchetti & Curtis, 2006). Because ASD represents an extremely heterogeneous group of disorders that differ in cause, course, response to treatment, and outcome, a better understanding of biological processes that operate in the context of treatment and prevention studies will lead to more targeted intervention approaches that are designed for specific subtypes of ASD. By tailoring the interventions in this way, it is hoped that the lives of more individuals with ASD and their families will be substantially improved.

References

Adrien, J. L., Lenoir, P., Martineau, J., Perrot, A., Hameury, L., Larmande, C., et al. (1993). Blind ratings of early symptoms of autism based upon family home movies. *Journal of the American Academy of Child & Adolescent Psychiatry, 32*, 617–626.

Ashwood, P., & Van de Water, J. (2004). A review of autism and the immune response. *Clinical & Developmental Immunology, 11*, 165–174.

August, G. J., Stewart, M. A., & Tsai, L. (1981). The incidence of cognitive disabilities in the siblings of autistic children. *British Journal of Psychiatry, 138*, 416–422.

Auranen, M., Vanhala, R., Varilo, T., Ayers, K., Kempas, E., Ylisaukko-oja, T., et al. (2002). A Genomewide screen for autism-spectrum disorders: Evidence for a major susceptibility locus on chromosome 3q25–27. *American Journal of Human Genetics, 71*, 777–790.

Bailey, A., Le Couteur, A., Gottesman, I., Bolton, P., Simonoff, E., Yuzda, E., et al. (1995). Autism as a strongly genetic disorder: Evidence from a British twin study. *Psychological Medicine, 25*, 63–77.

Bailey, A., Luthert, P., Dean, A., Harding, B, Janota, I., Montgomery, M., et al. (1998). A clinicopathological study of autism. *Brain, 121*, 889–905.

Bailey, A., Phillips, W., & Rutter, M. (1996). Autism: Towards an integration of clinical, genetic, neuropsychological, and neurobiological perspectives. *Journal of Child Psychology and Psychiatry, 37*, 89–126.

Bakermans-Kranenburg, M. J., Van Ijzendoorn, M. H., & Juffer, F. (2003). Less is more: Meta-analysis of sensitivity and attachment interventions in early childhood. *Psychological Bulletin, 129*, 195–215.

Baranek, G. T. (1999). Autism during infancy: A retrospective video analysis of sensory–motor and social behaviours at 9–12 months of age. *Journal of Autism and Developmental Disorders, 29*, 213–224.

Barrett, S., Beck, J. C., Bernier, R., Bisson, E., Braun, T. A., Casavant, T. L., et al. (1999). An autosomal genomic screen for autism. *American Journal of Medical Genetics, 88*, 609–615.

Bauman, M., & Kemper, T. L. (1985). Histoanatomic observations of the brain in early infantile autism. *Neurology, 35*, 866–874.

Bauman, M. L., & Kemper, T. L. (2005). Neuroanatomic observations of the brain in autism: A review and future directions. *International Journal of Developmental Neuroscience, 23*, 183–187.

Belmonte, M. K., Cook, E. H., Anderson, G. M., Rubenstein, J. l. R., Greenough, W. R., Beckel-Mitchener, A., et al. (2004). Autism as a disorder of neural information processing: Directions for research and targets for therapy. *Molecular Psychiatry, 9*, 646–663.

Benaroya-Milshtein, N., Hollander, N., Apter, A., Kukulansky, T., Raz, N., Wilf, A., et al. (2004). Environmental enrichment in mice decreases anxiety, attenuates stress responses and enhances natural killer cell activity. *European Journal of Neuroscience, 20*, 1341–1347.

Birnbrauer, J. S., & Leach, D. J. (1993). The Murdoch Early Intervention Program after 2 years. *Behavior Change, 10*, 63–74.

Black, L. S., deRegnier, R., Long, J., Georgieff, M. K., & Nelson, G., (2004). Electrographic imaging of recognition memory in 34–38 week gestation intrauterine growth restricted newborns. *Experimental Neurology, 190*, S72–S83.

Blatt, G. J., Fitzgerald, C. M., Guptill, J. T., Booker, A. B., Kemper, T. K., & Bauman, M. L. (2001). Density and distribution of hippocampal neurotransmitter receptors in autism: An autoradiographic study. *Journal of Autism and Developmental Disorders, 31*, 537–543.

Bolton, P., MacDonald, H., Pickles, A., Rios, P., Goode, S., Crowson, M., et al. (1994). A case–control family history study of autism. *Journal of Child Psychology and Psychiatry, 35*, 877–900.

Boucher, J., & Lewis, V. (1992). Unfamiliar face recognition in relatively able autistic children. *Journal of Child*

Psychology and Psychiatry and Allied Disciplines, 33, 843–859.

Boucher, J., Lewis, V., & Collis, G. (1998). Familiar face and voice matching and recognition in children with autism. *Journal of Child Psychology and Psychiatry, 39,* 171–181.

Bredy, T. W., Humpartzoomian, R. A., Cain, D. P., & Meaney, M. J. (2003). Partial reversal of the effect of maternal care on cognitive function through environmental enrichment. *Neuroscience, 118,* 571–576.

Brooks, R., & Meltzoff, A. N. (2005). The development of gaze following and its relation to language. *Developmental Science, 8,* 535–543.

Bruner, J. (1983). *Child's talk: Learning to use language.* Oxford: Oxford University Press.

Bryson, S. E., McDermott, C., Rombough, V., Brian, J., & Zwaigenbaum, L. (2007). The Autism Observation Scale for Infants: Scale development and reliability data. *Journal of Autism and Developmental Disorders.*

Bryson, S. E., Zwaigenbaum, L., Brian, J., Roberts, W., Szatmari, P., Rombough, V., et al. (2007). A prospective case series of high-risk infants who developed autism. *Journal of Autism and Developmental Disorders, 37,* 12–24.

Buxbaum, J. D., Silverman, J. M., Smith, C. J., Kilifarski, M., Reichert, J., Hollander, E., et al. (2001). Evidence for a susceptibility gene for autism on chromosome 2 and for genetic heterogeneity. *American Journal of Human Genetics, 68,* 1514–1520.

Caldji, C., Tannenbaum, B., Sharma, S., Francis, D., Plotsky, P. M., & Meaney, M. J. (1998). Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. *Proceedings of the National Academy of Sciences of the United States of America, 95,* 5335–5340.

Campbell, D. B., Sutcliffe, J. S., Ebert, P. J., Militerni, R., Bravaccio, C., Trillo, S., et al. (2006). A genetic variant that disrupts MET transcription is associated with autism. *Proceedings of the National Academy of Sciences of the United States of America, 103,* 16834–16839.

Cantor, R. M., Kono, N., Duvall, J. A., AlvarezRetuerto, A., Stone, J. L., Alarcon, M., et al. (2005). Replication of autism linkage: Fine-mapping peak at 17q21. *American Journal of Human Genetics, 76,* 1050–1056.

Casanova, M. F. (2004). White matter volume increase and minicolumns in autism. *Annals of Neurology, 56,* 453.

Casanova, M. F., Buxhoeveden, D. P., Switala, A. E., & Roy, E. (2002). Minicolumnar pathology in autism. *Neurology, 58,* 428–432.

Castellanos, F. X., & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. *Nature Reviews. Neuroscience, 3,* 617–628.

Caston, J., Devulder, B., Jouen, F., Lalonde, R., Delhaye-Bouchaud, N., & Mariani, J. (1999). Role of an enriched environment on the restoration of behavioral deficits in Lurcher mutant mice. *Developmental Psychobiology, 35,* 291–303.

Chandler, S., Christie, P., Newson, E., & Prevezer, W. (2002). Developing a diagnostic and intervention package for 2- to 3-year-olds with autism: Outcomes of the frameworks for communication approach. *Autism, 6,* 47–69.

Cheh, M. A., Millonig, J. H., Roselli, L. M., Ming, X., Jacobsen, E. Kamdar, S., et al. (2006). En2 knockout mice display neurobehavioral and neurochemical alterations relevant to autism spectrum disorder. *Brain Research, 1116,* 166–176.

Cicchetti, D., & Cohen, D. J. (1995). Perspectives on developmental psychopathology. In D. Cicchetti & D. J. Cohen (Eds.), *Developmental psychopathology: Vol. 1. Theory and methods* (pp. 3–22). New York: Wiley.

Cicchetti, D., & Curtis, W. J. (2006). The developing brain and neural plasticity: Implications for normality, psychopathology, and resilience. In D. Cicchetti & D. Cohen (Eds.), *Developmental psychopathology: Developmental neuroscience* (Vol. 2, 2nd ed.). New York: Wiley.

Cohen, H., Amerine-Dickens, M., & Smith, T. (2006). Early intensive behavioral treatment: Replication of the UCLA model in a community setting. *Journal of Development and Behavioral Pediatrics, 27,* S145–S155.

Courchesne, E. (1997). Brainstem, cerebellar and limbic neuroanatomical abnormalities in autism. *Current Opinion in Neurobiology, 7,* 269–278.

Courchesne, E. (2004). Brain development in autism: Early overgrowth followed by premature arrest of growth. *Mental Retardation and Developmental Disabilities Research Reviews, 10,* 106–111.

Courchesne, E., Carper, R., & Akshoomoff, N. (2003). Evidence of brain overgrowth in the first year of life in autism. *Journal of the American Medical Association, 290,* 337–344.

Courchesne, E., Karns, C., Davis, H. R., Ziccardi, R., Carper, R., Tigue, Z., et al. (2001). Unusual brain growth patterns in early like in patients with autistic disorder: An MRI study. *Neurology, 57,* 245–254.

Courchesne, E., & Pierce, K. (2005). Brain overgrowth in autism during a critical time in development: Implications for frontal pyramidal neuron and interneuron development and connectivity. *International Journal of Developmental Neuroscience, 23,* 153–170.

Croen, L. A., Grether, J. K., Yoshida, C. K., Odouli, R., & Van de Water, J. (2005). Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: A case-control study. *Archives of Pediatrics and Adolescent Medicine, 159,* 151–157.

Croughan, M., Schembri, M., Bernstein, N., Chamberlain, N., Purcell, N., & Camarano, L. (2006). *Maternal and childhool outcomes following infertility and infertility treatments.* Paper presented at the American Society for Reproductive Medicine Annual Scientific Meeting, New Orleans, October 21–25, 2006.

Dawson, G. (Ed.). (1989). *Autism: Nature, diagnosis and treatment.* New York: Guilford Press.

Dawson, G., Carver, L., Meltzoff, A. N., Panagiotides, H., McPartland, J., & Webb, S. J. (2002). Neural correlates of face and object recognition in young children with autism spectrum disorder, developmental delay, and typical development. *Child Development, 73,* 700–717.

Dawson, G., & Faja, S. (in press). Autism spectrum disorders: A developmental perspective. In T. P. Beauchaine & S. P. Hinshaw (Eds.), *Child and adolescent psychopathology.* Hoboken, NJ: Wiley.

Dawson, G., Frey, K., Panagiotides, H., Osterling, J., & Hessl, D. (1997). Infants of depressed mothers exhibit atypical frontal brain activity: A replication and extension of previous findings. *Journal of Child Psychology and Psychiatry, 38,* 179–186.

Dawson, G., Frey, K., Panagiotides, H., Yamada, E., Hessl, D., & Osterling, J. (1999). Infants of depressed mothers exhibit atypical frontal electrical brain activity during interactions with mother and with a familiar, non-depressed adult. *Child Development, 70,* 1058–1066.

Dawson, G., Hill, D., Galpert, L., Spencer, A., & Watson, L. (1990). Affective exchanges between young autistic children and their mothers. *Journal of Abnormal Child Psychology, 18*, 335–345.

Dawson, G., Meltzoff, A. N., Osterling, J., Rinaldi, J., & Brown, E. (1998). Children with autism fail to orient to naturally occurring social stimuli. *Journal of Autism and Developmental Disorders, 28*, 479–485.

Dawson, G., Munson, J., Estes, A., Osterling, J., McPartland, J., Toth, K., et al. (2002). Neurocognitive function and joint attention ability in young children with autism spectrum disorder versus developmental delay. *Child Development, 73*, 345–358.

Dawson, G., Munson, J., Webb, S. J., Nalty, T., Abbott, R., & Toth, K. (2007). Rate of head growth decelerates and symptoms worsen in the second year of life in autism. *Biological Psychiatry, 61*, 458–464.

Dawson, G., & Osterling, J. (1997). Early intervention in autism: Effectiveness and common elements of current approaches. In E. Guralnick (Ed.), *The effectiveness of early intervention: Second generation research* (pp. 307–326). Baltimore, MD: Brookes.

Dawson, G., Osterling, J., Meltzoff, A. N., & Kuhl, P. (2000). Case study of the development of an infant with autism from birth to 2 years of age. *Journal of Applied Developmental Psychology, 21*, 299–313.

Dawson, G., Sterling, L., & Faja, S. (in press). Autism spectrum disorders. In J. De Haan & J. Gunnar (Eds.), *Handbook of developmental social neuroscience*. New York: Guilford Press.

Dawson, G., Toth, K., Abbott, R., Osterling, J., Munson, J., Estes, A., et al. (2004). Early social attention impairments in autism: Social orienting, joint attention, and attention to distress. *Developmental Psychology, 40*, 271–283.

Dawson, G., Webb, S., Carver, L., Panagiotides, H., & McPartland, J. (2004). Young children with autism show atypical brain responses to fearful versus neutral facial expressions. *Developmental Science, 7*, 340–359.

Dawson, G., Webb, S. J., Estes, A., Munson, J., & Faja, S. (2008). *Electrophysiological indices of altered emotional face processing in parents of children with autism*. Manuscript submitted for publication.

Dawson, G., Webb, S., & McPartland, J. (2005). Understanding the nature of face processing impairment in autism: Insights from behavioral and electrophysiological studies. *Developmental Neuropsychology, 27*, 403–424.

Dawson, G., Webb, S., Schellenberg, G. D., Aylward, E., Richards, T., Dager, S., et al. (2002). Defining the broader phenotype of autism: Genetic, brain, and behavioral perspectives. *Development and Psychopathology, 14*, 581–611.

Dawson, G., Webb, S. J., Wijsman, E., Schellenberg, G., Estes, A., Munson, J., et al. (2005). Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: Implications for a model of abnormal development of social brain circuitry in autism. *Development and Psychopathology, 17*, 679–697.

Dawson, G., & Zanolli, K. (2003). Early intervention and brain plasticity in autism. In G. Bock & J. Goode (Eds.), *Autism: Neural bases and treatment possibilities. Novartis Foundation Symposium* 251 (pp. 266–280). Chichester: Wiley.

de Haan, M., & Nelson, C. A. (1997). Recognition of the mother's face by 6-month-old infants: A neurobehavioral study. *Child Development, 68*, 187–210.

DeFelipe, J., Hendry, S. H., Hashikawa, T., Molinari, M., & Jones, E. G. (1990). A microcolumnar structure of monkey cerebral cortex revealed by immunocyochimical studies of double bouquet cell axons. *Neuroscience, 23*, 622–631.

Devlin, B., Cook, E. H., Jr., Coon, H., Dawson, G., Grigorenko, E. L., McMahon, W., et al. (2005). Autism and the serotonin transporter: The long and short of it. *Molecular Psychiatry, 10*, 1110–1116.

Diamond, M. C., Rosenzweig, M. R., Bennett, E. L., Lindner, B., & Lyon, L. (1972). Effects of environmental enrichment and improverishment on rat cerebral cortex. *Journal of Neurobiology, 3*, 47–64.

Drew, A., Baird, G., Baron-Cohen, S., Cox, A., Slonims, V., Wheelwright, S., et al. (2002). A pilot randomized control trial of a parent training intervention for pre-school children with autism: Preliminary findings and methodological challenges. *European Child & Adolescent Psychiatry, 11*, 266–272.

Duffy, S. N., Craddock, K. J., Abel, T., & Nguyen, P. V. (2001). Environmental enrichment modifies the PKA-dependence of hippocampal LTP and improves hippocampus-dependent memory. *Learning and Memory, 8*, 26–34.

Durand, C. M., Betancur, C., Boeckers, T. M., Bockmann, J., Chaste, P., Fauchereau, F., et al. (2007). Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nature Genetics, 39*, 25–27.

Elder, L., Dawson, G., Toth, K., Fein, D., & Munson, J. (2008). *Head circumference as an early predictor of autism symptoms in young siblings of children with autism*. Manuscript submitted for publication.

Escorihuela, R. M., Tobena, A., & Fernandez-Teruel, A. (1995). Environmental enrichment and postnatal handling prevent spatial learning deficits in aged hypoemotional (Roman high-avoidance) and hyperemotional (Roman low-avoidance) rats. *Learning and Memory, 2*, 40–48.

Fatemi, S. H., Earle, J., Kanodia, R., Kist, D., Emamian, E. S., Patterson, P. H., et al. (2002). Prenatal viral infection leads to pyramidal cell atrophy and macrocephaly in adulthood: implications for genesis of autism and schizophernia. *Cellular and Molecular Neurobiology, 22*, 25–33.

Fatemi, S. H., & Halt, A. R. (2001). Altered levels of bcl2 and p53 proteins in parietal cortex reflect deranged apoptotic regulation in autism. *Synapse, 42*, 281–284.

Faverjon, S., Silveira, D. C., Fu, D. D., Cha, B. H., Akman, C., Hu, Y., et al. (2002). Beneficial effects of enriched environment following status epilepticus in immature rats. *Neurology, 59*, 1356–1364.

Fenske, E. C., Zalenski, S., Krantz, P. J., & McClannahan, L. E. (1985). Age at intervention and treatment outcome for autistic children in a comprehensive intervention program. *Analysis and Intervention in Developmental Disabilities, 5*, 49–58.

Floeter, M. K., & Greenough, W. T. (1979). Cerebellar plasticity: Modification of Purkinje cell structure by differential rearing in monkeys. *Science, 206*, 227–229.

Folstein, S., & Rutter, M. (1977a). Genetic influences and infantile autism. *Nature, 265*, 726–728.

Folstein, S., & Rutter, M. (1977b). Infantile autism: A genetic study of 21 twin pairs. *Journal of Child Psychology and Psychiatry, 18*, 297–321.

Foster, T. C., Gagne, J., & Massicotte, G. (1996). Mechanism of altered synaptic strength due to experience: Relation to long-term potentiation. *Brain Research, 736*, 243–250.

Francis, D. D., Diorio, J., Plotsky, P. M., & Meaney, M. J. (2002). Environmental enrichment reverses the effects of maternal separation on stress reactivity. *Journal of Neuroscience, 22*, 7840–7843.

Friedman, S. D., Shaw, D. W., Artru, A. A., Dawson, G., Petropoulos, H., & Dager, S. R. (2006). Gray and white matter brain chemistry in young children with autism. *Archives of General Psychiatry, 63*, 786–794.

Friedman, S. D., Shaw, D. W., Artru, A. A., Richards, T. L., Gardner, J., Dawson, G., et al. (2003). Regional brain chemical alterations in young children with autism spectrum disorder. *Neurology, 60*, 100–107.

Garber, K. (2007). Autism's cause may reside in abnormalities at the synapse. *Science, 317*, 190–191.

Gepner, B., de Gelder, B., & de Schonen, S. (1996). Face processing in autistics: Evidence for a generalized deficit? *Child Neuropsychology, 2*, 123–139.

Gillberg, C., & de Souza, L. (2002). Head circumference in autism, Asperger syndrome, and ADHD: A comparative study. *Developmental Medicine and Child Neurology, 44*, 296–300.

Gingrich, B., Liu, Y., Cascio, C., Wang, Z., & Insel, T. R. (2000). Dopamine D2 receptors in the nucleus accumbens are important for social attachment in female prairie voles. *Behavioral Neuroscience, 114*, 173–183.

Glass, M., van Dellen, A., Blakemore, C., Hannan, A. J., & Faull, R. L. (2004). Delayed onset of Huntington's disease in mice in an enriched environment correlates with delayed loss of cannabinoid CB1 receptors. *Neuroscience, 123*, 207–212.

Green, G., Brennan, L. C., & Fein, D. (2002). Intensive behavioral treatment for a toddler at high risk for autism. *Behavior Modification, 26*, 69–102.

Greenough, W. T., Volkmar, F. R., & Juraska, J. M. (1973). Effects of rearing complexity on dendritic branching in frontotemporal and temporal cortex of the rat. *Experimental Neurology, 41*, 371–378.

Grelotti, D., Gauthier, I., & Schultz, R. (2002). Social interest and the development of cortical face specialization: what autism teaches us about face processing. *Developmental Psychobiology, 40*, 213–225.

Hamm, R. J., Temple, M. D., O'Dell, D. M., Pike, B. R., & Lyeth, B. G. (1996). Exposure to environmental complexity promotes recovery of cognitive function after traumatic brain injury. *Journal of Neurotrauma, 13*, 41–47.

Harris, S. L., & Handleman, J. S. (2000). Age and IQ at intake as predictors of placement for young children with autism: A four- to six-year follow-up. *Journal of Autism and Developmental Disorders, 30*, 137–142.

Harris, S. L., Handleman, J. S., Gordon, R., Kristoff, B., & Fuentes, F. (1991). Changes in cognitive and language functioning of preschool children with autism. *Journal of Autism and Developmental Disorders, 21*, 281–290.

Haxby, J. V., Horwitz, B., Ungerleider, L. G., Maisog, J. M., Pietrini, P., & Grady, C. (1994). The functional organization of human extrastriate cortex: A PET-rCBF study of selective attention to faces and locations. *Journal of Neuroscience, 14*, 6336–6353.

Haxby, J. V., Ungerleider, L. G., Clark, V. P., Schouten, J. L., Hoffman, E. A., & Martin, A. (1999). The effect of face inversion on activity in human neural systems for face and object perception. *Neuron, 22*, 189–199.

Hazlett, H. C., Poe, M., Gerig, G., Smith, R. G., Provenzale, J., Ross, A., et al. (2005). Magnetic resonance imaging and head circumference study of brain size in autism: Birth through age 2 years. *Archives of General Psychiatry, 62*, 1366–1376.

Hebb, D. O. (1947). The effects of early experience on problem-solving at maturity. *American Psychologist, 2*, 306–307.

Herbert, M. R., Russo, J. P., Yang, S., Roohi, J., Blaxill, M., Kahler, S. G., et al. (2006). Autism and environmental genomics. *Neuro Toxicology, 27*, 671–684.

Hollander, E., Bartz, J., Chaplin, W., Phillips, A., Sumner, J., Soorya, L., et al. (2007). Oxytocin increases retention of social cognition in autism. *Biological Psychiatry, 61*, 498–503.

Hollander, E., Novotny, S., Hanratty, M., Yaffe, R., DeCaria, C. M., Aronowitz, B. R., et al. (2003). Oxytocin infusion reduces repetitive behavior in adults with autistic and Asperger's disorders. *Neuropsychopharmacology, 28*, 193–198.

Hood, B. M., & Atkinson, J. (1990). Sensory visual loss and cognitive deficits in the selective attention system of normal infants and neurological impaired children. *Development Medicine and Child Neurology, 32*, 1067–1077.

Horowitz, B., Rumsey, J., Grady, C., & Rappoport, S. (1988). The cerebral metabolic landscape in autism: Intercorrelations of regional glucose utilization. *Archives of Neurology, 4*, 749–755.

Howard, J. S., Sparkman, C. R., Cohen, H. G., Green, G., & Stanislaw, H. A., (2005). Comparison of intensive behavior analytic and eclectic treatments for young children with autism. *Research in Developmental Disabilities, 26*, 359–383.

Ingersoll, B., Schreibman, L., & Stahmer, A. (2001). Brief report: Differential treatment outcomes for children with autistic spectrum disorder based on level of peer social avoidance. *Journal of Autism and Developmental Disorders, 31*, 343–350.

Insel, T. R., & Fernald, R. D. (2004). How the brain processes social information: Searching for the social brain. *Annual Review of Neuroscience, 27*, 697–722.

Insel, T. R., & Hulihan, T. J. (1995). A gender-specific mechanism for pair bonding: Oxytocin and partner preference formation in monogamous voles. *Behavioral Neuroscience, 109*, 782–789.

International Molecular Genetic Study of Autism Consortium (IMGSAC). (1998). A full genome screen for autism with evidence for linkage to a region on chromosome 7q. *Human Molecular Genetics, 7*, 571–578.

International Molecular Genetic Study of Autism Consortium (IMGSAC). (2001a). Further characterization of the autism susceptibility locus AUTS1 on chromosome 7q. *Human Molecular Genetics, 10*, 973–982.

International Molecular Genetic Study of Autism Consortium (IMGSAC). (2001b). A genomewide screen for autism: Strong evidence for linkage to chromosomes 2q, 7q, and 16p. *American Journal of Human Genetics, 69*, 570–581.

Jacob, S., Brune, C. W. Carter, C. S., Leventhal, B. L., Lord, C., & Cook, E. H. (2007). Association of the oxytocin receptor gene (*OXTR*) in Caucasion children and adolescents with autism. *Neuroscience Letters, 417*, 6–9.

Jamain, S., Quach, H., Betancur, C., Rastam, M., Colineaux, C., Gillberg, I. C., et al. (2003). Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nature Genetics, 34*, 27–29.

James, S. J., Cutler, P., Melnyk, S., Jernigan, S., Janak, L., Gaylor, D. W., et al. (2004). Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. *American Journal of Clinical Nutrition, 80*, 1611–1617.